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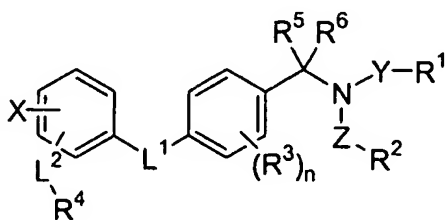
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(54) Title: CANNABINOID RECEPTOR LIGANDS



(I)

(57) Abstract: There are disclosed compounds of the formula
(I) a prodrug thereof, or a pharmaceutically acceptable salt,
solvate or stereoisomer of the compound or of said prodrug;
which exhibit anti-inflammatory and immunomodulatory activity.
Also disclosed are pharmaceutical compositions containing
said compounds and methods of using the compounds for the
treatment of various diseases and conditions.

CANNABINOID RECEPTOR LIGANDS

BACKGROUND OF THE INVENTION

This invention relates to cannabinoid receptor ligands and, more particularly, to compounds that bind to cannabinoid (CB₂) receptors. Compounds according to the present invention generally exhibit anti-inflammatory and immunomodulatory activity and are useful in treating conditions characterized by inflammation and immunomodulatory irregularities. Examples of conditions which may be treated include, but are not limited to, rheumatoid arthritis, asthma, allergy, psoriasis, Crohn's disease, systemic lupus erythematosus, multiple sclerosis, diabetes, cancer, glaucoma, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, and nephritis. The invention also relates to pharmaceutical compositions containing said compounds.

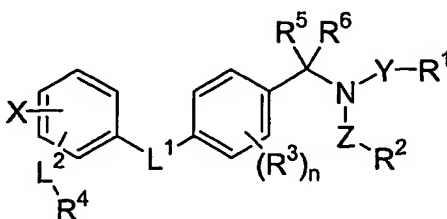
Cannabinoid receptors belong to the superfamily of G-protein coupled receptors. They are classified into the predominantly neuronal CB₁ receptors and the predominantly peripheral CB₂ receptors. While the effects of CB₁ receptors are principally associated with the central nervous system, CB₂ receptors are believed to have peripheral effects related to bronchial constriction, immunomodulation and inflammation. As such, a selective CB₂ receptor binding agent is expected to have therapeutic utility in the control of diseases associated with inflammation, immunomodulation and bronchial constriction such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, diabetes, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, nephritis, inflammatory disorders of the lungs and gastrointestinal tract, and respiratory tract disorders such as reversible airway obstruction, chronic asthma and bronchitis (see, e.g., R.G. Pertwee, *Curr. Med. Chem.* 6(8), (1999), 635).

Various compounds have reportedly been developed which interact with CB₂ receptors and/or which have, *inter alia*, anti-inflammatory activity associated with cannabinoid receptors. See, e.g., U.S. Pat. Nos. 5,338,753, 5,462,960, 5,532,237, 5,925,768, 5,948,777, 5,990,170, 6,013,648 and 6,017,919.

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SUMMARY OF THE INVENTION

This invention relates to compounds of formula I:



- 5 a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein:

R^1 is H, alkyl, haloC₁-C₆ alkyl, cycloalkyl, cycloalkylNH-, arylalkyl, heterocycloalkyl, heteroaryl, N(R²)₂, or NR²aryl, unsubstituted aryl or aryl substituted
10 with one to three X;

R^2 is the same or different in each occurrence and is independently selected from H or C₁-C₆ alkyl;


R^3 is H, C₁-C₆ alkyl, Cl, F, CF₃, OCF₂H, OCF₃, OH or C₁-C₆ alkoxy;

R^4 is H, C₁-C₆ alkyl, C₁-C₆ alkoxy, cycloalkyl, alkenyl, aryl, benzyl, heteroaryl,
15 heterocycloalkyl, arylNH-, heteroarylNH-, cycloalkylNH-, N(R²)₂, or NR²aryl, said alkyl, alkoxy, cycloalkyl, alkenyl, phenyl or heteroaryl optionally substituted with one to three X;

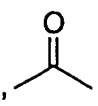
R^5 is H or C₁-C₆ alkyl;

R^6 is H or C₁-C₆ alkyl; or

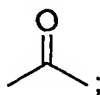
20 R^5 and R^6 taken together with the carbon atom form a carbonyl group;

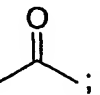
L^1 is C₁-C₆ alkylene, C₂-C₆ alkenylene, C(R²)₂, , -CHOR²-, NOR⁵-, -SO₂-, -SO-, -S-, -O-, -NR²-, -C(O)NR²-, -NR²C(O)-, -CHCF₃- or -CF₂-;

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L^2 is a covalent bond, C_1 - C_6 alkylene, $-C(R^2)_2-$, , $-CHOR^2-$, $-C(R^2)OH$, NOR^5- , $-SO_2-$, $-NR^2SO_2-$, $-SO-$, $-S-$, $-O-$, $-SO_2NR^2-$, $-N(R^2)-$, $-C(O)NR^2-$ or $-NR^2C(O)-$;

X is the same or different, and is independently selected from H, halogen, CF_3 , CN, OCF_2H , OCF_2CF_3 , OCF_3 , OR^2 , C_1 - C_6 alkyl, cycloalkyl, cycloalkoxy, C_1 - C_6 alkoxy, 5 alkoxy C_1 - C_6 alkoxy, O-cycloalkyl, cycloalkylamino, cycloalkylalkoxy, heteroalkyl, $-OSO_2R^2$, $-COOR^2$, $-CON(R^2)_2$, NHR^2 , arylNH-, $N(R^2)_2$, or NR^2 aryl;

Y is a covalent bond, $-CH_2-$, $-SO_2-$, or ;

Z is a covalent bond, $-CH_2-$, $-SO_2-$ or ; or

Y, R^1 , Z and R^2 can be taken together with the nitrogen atom to form a 10 heterocycloalkyl; with the proviso that if Y is a covalent bond, R^1 cannot form a N-N bond with the nitrogen atom; and
n is an integer of 0 to 4.

Cannabinoid receptor ligands according to the present invention have anti- 15 inflammatory activity and/or immunomodulatory activity and are useful in the treatment of various medical conditions including, e.g., cutaneous T cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, 20 psoriasis, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, Crohn's disease, inflammatory bowel disease, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) or bronchitis. It is contemplated that a compound of this invention may be useful in treating more than one of the diseases listed.

25 Additionally, a compound of the present invention may be co-administered or used in combination with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, azathioprine, leflunomide, penicillamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. They may also be co-administered with or used in combination with NSAIDs such as piroxicam, naproxen,

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indomethacin, ibuprofen and the like; COX-2 selective inhibitors such as Vioxx® and Celebrex®; COX-1 inhibitors such as Feldene; immunosuppressives such as steroids, cyclosporine, Tacrolimus, rapamycin, muromonab-CD3 (OKT3), Basiliximab and the like; biological response modifiers (BRMs) such as Enbrel, Remicade, IL-1

5 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, TACE inhibitors, chemokine receptor antagonists, Thalidomide and other small molecule inhibitors of pro-inflammatory cytokine production. They may also be co-administered with or used in combination with H1 antagonists such as Claritin, Clarinex, Zyrtec,

10 Allegra, Benadryl, and other H1 antagonists. Other drugs that the compounds of the invention may be co-administered or used in combination with include Anaprox, Arava, Arthrotec, Azulfidine, Aspirin, Cataflam, Celestone Soluspan, Clinoril, Cortone Acetate, Cuprimine, Daypro, Decadron, Depen, Depo-Medrol, Disalcid, Dolobid, Naprosyn, Gengraf, Hydrocortone, Imuran, Indocin, Lodine, Motrin, Myochrysine,

15 Nalfon, Naprelan, Neoral, Orudis, Oruvail, Pediapred, Plaquenil, Prelone, Relafen, Solu-Medrol, Tolectin, Trilisate and Volataren. These include any formulations of the above-named drugs.

For the treatment of multiple sclerosis, the compounds of the invention may be co-administered or used in combination with Avonex, Betaseron, Rebif and Copaxone.

20 These include any formulations of the above-named drugs.

For the treatment of psoriasis, the compounds of the invention may be co-administered or used in combination with steroids, methotrexate, cyclosporin, Xanelin, Amivere, Vitamin D analogs, topical retinoids, anti-TNF- α compounds and other drugs indicated for this condition. These include any formulations of the above-named

25 drugs.

For the treatment of asthma, the compounds of the invention may be co-administered or used in combination with Singulair, Accolate, Albuterol, and other drugs indicated for this disease. These include any formulations of the above-named drugs.

30 For the treatment of inflammatory bowel disease or Crohn's disease, the compounds of the invention may be co-administered or used in combination with sulfasalazine, budesonide, mesalamine and other drugs indicated for these diseases. These include any formulations of the above-named drugs.

In another aspect, the invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

5 Unless otherwise defined, the following definitions shall apply throughout the specification and claims.

When any variable (e.g., R²) occurs more than one time in any constituent, its definition in each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such
10 combinations result in stable compounds.

"Alkyl" means straight or branched alkyl chains of 1 to 12 carbon atoms. The term includes the isomers thereof such as isopropyl, isobutyl, sec-butyl, etc.

"Haloalkyl" means alkyl having 1 or more halo atoms.

"Heteroalkyl" means straight or branched alkyl chain comprised of from 1 to 12
15 carbon atoms and 1 or more heteroatoms independently selected from the group consisting of N, O and S.

"Cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings, including, but not limited to cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, and adamantyl among others.

20 "Heterocycloalkyl" means cycloalkyl containing one or more heteroatoms.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising from 6 to 14 carbon atoms. Non-limiting examples include phenyl, naphthyl, indenyl, tetrahydronaphthyl and indanyl.

"Arylalkyl" means a group in which the aryl and alkyl are as previously
25 described. Non-limiting examples of suitable arylalkyl groups include benzyl, 2-phenethyl and naphthlenylmethyl. The bond to the parent moiety is through the alkyl.

"Heteroaryl" means a single ring or benzofused heteroaromatic group of 5 to 10 atoms comprised of 1 to 9 carbon atoms and 1 or more heteroatoms independently selected from the group consisting of N, O and S. N-oxides of the ring nitrogens are
30 also included, as well as compounds wherein a ring nitrogen is substituted by a C₁-C₆ alkyl group to form a quaternary amine. Examples of single-ring heteroaryl groups are pyridyl, oxazolyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl,

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tetrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazinyl, pyrimidyl, pyridazinyl and triazolyl. Examples of benzofused heteroaryl groups are indolyl, quinolyl, isoquinolyl, phthalazinyl, benzothienyl (i.e., thionaphthenyl), benzimidazolyl, benzofuranyl, benzoxazolyl and benzofurazanyl. All positional isomers are contemplated, e.g., 2-
 5 pyridyl, 3-pyridyl and 4-pyridyl.

"Alkoxy" means an alkyl radical attached by an oxygen, i.e., alkoxy groups having 1 to 9 carbon atoms.

"Alkenyl" means straight or branched chains of carbon atoms having one or more double bonds in the chain, conjugated or unconjugated.

10 "Oxime" means a $\text{CH}(\text{:NOH})$ radical containing moiety.

"Halogen", "halogenated" or "halo" refers to fluorine, chlorine, bromine or iodine radicals.

The term "prodrug," as used herein, represents compounds which are rapidly transformed in vivo to the parent compound of the above formula, for example, by
 15 hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

20 Linker groups such as L^1 , L^2 , Y and Z are divalent.

In a preferred group of compounds of formula I,

L^1 is $-\text{SO}_2-$, $-\text{CH}_2-$, $-\text{CHCH}_3-$, $-\text{C}(=\text{O})-$, $-\text{C}=\text{NOR}^2-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CHOH}-$, $-\text{O}-$, $-\text{S}-$ or $-\text{S}=\text{O}$;



25 L^2 is $-\text{SO}_2-$, $-\text{C}(=\text{O})-$, $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{C}(\text{CH}_3)=\text{CH}_2-$, $-\text{NH}-$, $-\text{O}-$, $-\text{NHSO}_2-$, $-\text{NHC}(\text{O})-$ or $-\text{C}(\text{CH}_3)(\text{OH})-$;

R^1 is H, $-\text{CH}_3\text{NH}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{NHC}_3\text{H}_7$, $-\text{NHC}_2\text{H}_5$, $-\text{NHC}_4\text{H}_9$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{CF}_3$, $-\text{CH}(\text{CH}_3)_2$, thiophenyl, morpholinyl, cyclopropanyl, benzyl, naphthyl, $\text{C}(\text{CH}_3)_3$, NHphenyl, 3,5-difluorophenyl, phenyl, N-cyclopentyl or $\text{N}(\text{CH}_3)_2$;

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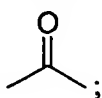
R^2 is H or CH_3 ;

R^4 is furanyl, pyridyl, pyrimidyl, thiophenyl, quinolyl, t-butoxy, alkoxy, cyclohexyl, phenyl, tolyl, C_3H_7 , dimethylpyrimidyl, trifluoromethoxyphenyl, morpholinylphenyl or CH_3 ; with the proviso that when R^4 is t-butoxy, L^2 must be

5 , $-CH_2-$, $-CHCH_3-$, $-C(CH_3)_2-$ or , all of the above optionally substituted with one to three substituents, which are the same or different and are independently selected from X;

R^5 and R^6 are independently H or CH_3 ;

X is H, Cl, CF_3 , OCH_3 , OCF_3 , OCF_2H , CH_3 or C_1-C_6 cycloalkyl;

10 Y is $-SO_2-$ or ;

Z is a covalent bond; or

R^1 , Y, R^2 and Z taken together with the nitrogen atom form a morpholinyl group.

15 In a more preferred embodiment of the invention,

L^1 is $-SO_2-$ or $-CH_2-$;

L^2 is $-SO_2-$;

R^1 is CH_3 or CF_3 ; and

20 R^4 is phenyl, pyrimidyl or pyridyl, said phenyl, pyrimidyl or pyridyl groups optionally substituted with one to three substituents independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, OH, CF_3 and halogen.

More preferably, the phenyl is substituted with OCH_3 or halogen selected from fluorine and chlorine.

25

Compounds of the invention may have at least one asymmetrical carbon atom and therefore all isomers, including diastereomers and rotational isomers are contemplated as being part of this invention. The invention includes (+)- and (-)- isomers in both pure form and in admixture, including racemic mixtures. Isomers can
30 be prepared using conventional techniques, either by reacting optionally pure or optically enriched starting materials or by separating isomers of a compound of

formula I. Those skilled in the art will appreciate that for some compounds of formula I, one isomer may show greater pharmacological activity than other isomers.

Compounds of formula I can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable
5 solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

Compounds of the invention with a basic group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic,
10 malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from
15 its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

Certain compounds of the invention are acidic (e.g., compounds where R^2 is a hydrogen covalently bonded to N). Acidic compounds according to the present
20 invention can form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, magnesium, zinc, lithium, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine, piperazines and other amines.

25 Compounds of the present invention are generally prepared by processes known in the art, for example by the processes described below.

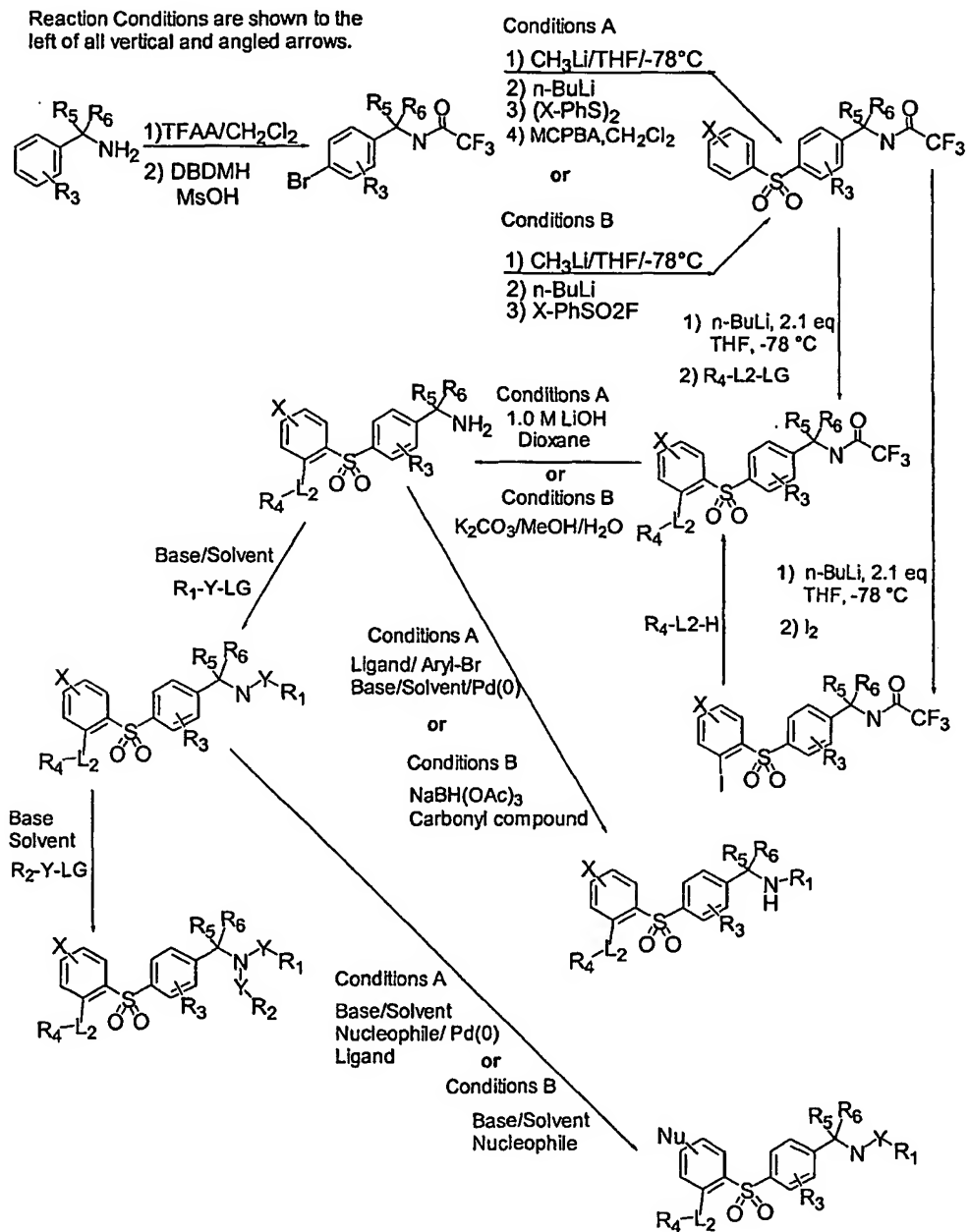
The following abbreviations are used in the procedures and schemes: aqueous (aq), anhydrous (anhyd), n-butyllithium (n-BuLi), dibromodimethylhydantoin (DBDMH), diisopropylethylamine (DIPEA), diethyl ether (Et_2O), dimethylacetamide (DMA),
30 dimethyl sulfoxide (DMSO), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ethanol (EtOH), ethyl acetate (EtOAc), 2-propanol (IPA), leaving group (LG), lithium hexamethyldisilazide (LHMDS), meta-chloroperoxybenzoic acid (MCPBA), methanesulfonic acid (MsOH), methanesulfonyl chloride (MsCl),

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N-iodosuccinamide (NIS), preparative thin layer chromatography on Merck- silica plates (PTLC), phenyl (Ph), pyridinium chlorochromate (PCC), pyridine (Py), trifluoroacetic anhydride (TFAA), triflic anhydride (Tf₂O), tetrahydrofuran (THF), silica gel chromatography (sgc), thin layer chromatography (TLC), room temperature (rt),
5 hours (h), minutes (min), molar (M), pounds per square inch (psi), and saturated aqueous sodium chloride solution (brine).

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General Scheme I Preparation of Aryl-Bis-Sulfone Compounds



5

Description of Reactions-General Scheme I

In step 1, trifluoroacetic anhydride is dissolved in a suitable inert solvent such as methylene chloride and reacted with a benzyl amine at room temperature for 1-5 hr. MsOH (2 eq) is added followed by DBDMH and the reaction mixture is stirred

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overnight at room temperature and subjected to aqueous work up. The crude product is recrystallized from a mixture of Et₂O and hexanes or purified via chromatography.

In step 2, the product of step 1 is dissolved in THF, cooled in a dry ice/IPA bath and treated with methyllithium then n-BuLi. The resulting dianion may be trapped with a sulfonyl fluoride or a disulfide. If a disulfide is the trapping agent, the resulting product is oxidized with MCPBA in CH₂Cl₂ at room temperature for 1-6 h. The product may be purified via chromatography or crystallization.

In step 3, the product of step 2 is dissolved in THF and treated with n-BuLi at -78 °C to form a dianion that is trapped with a suitable electrophile.

Alternatively, in step 3 the product of step 2 is dissolved in THF treated with n-BuLi at -78 °C to form a dianion which is trapped with iodine to provide the iodo substituted product. The product may be purified via sgc or crystallization. The iodo product can be converted to a similar product by nucleophilic aromatic substitution with a variety of nucleophiles, including amines, alcohols, and thiols.

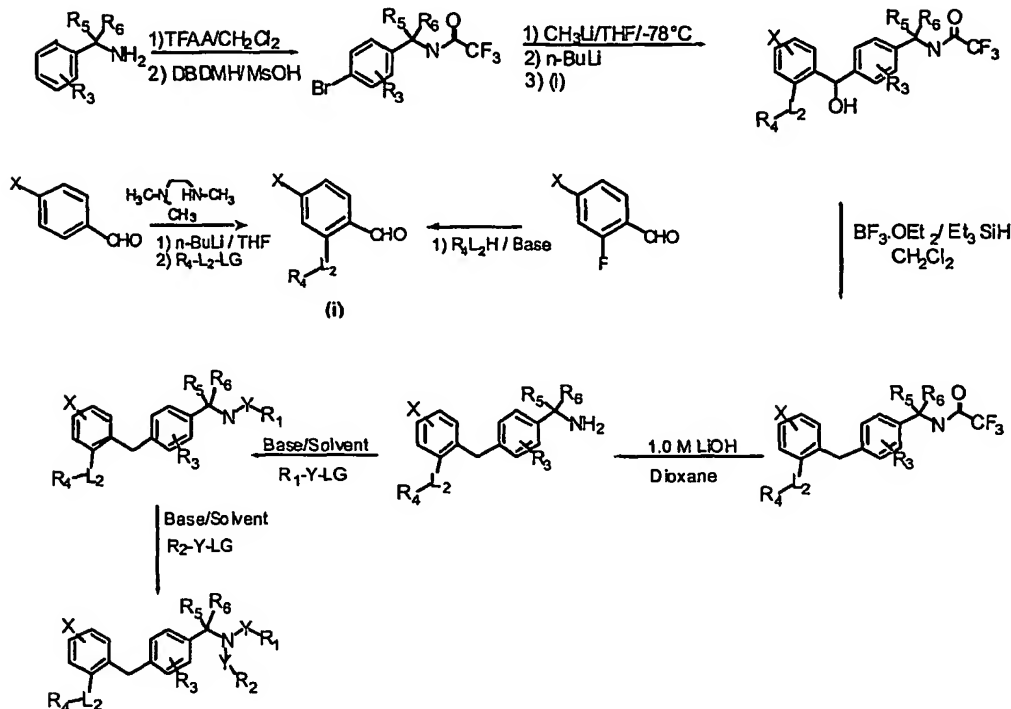
In step 4, the product of step 3 is dissolved in a suitable solvent such as dioxane, ethanol, methanol or THF and an alkali metal hydroxide or carbonate such as lithium hydroxide or potassium carbonate is added either as an aqueous solution or as a solid. The reaction mixture is stirred at room temperature for 0.5-24 h. The product may be purified via sgc or crystallization.

In step 5, a combination of the product of step 4 and a tertiary amine base was dissolved in a suitable solvent such as CH₂Cl₂ or dioxane, at room temperature, cooled, and a suitable electrophile is added. The reaction mixture is stirred between -78 °C and 100 °C for 0.5 to 48 h. The product may be purified via sgc or crystallization.

In step 6, the product of step 5 is dissolved in a suitable inert solvent such as THF or CH₂Cl₂ and treated with a suitable base such as NaH or triethylamine. An electrophile is added and the reaction mixture is stirred between 0 °C and 100°C for 0.5 to 48 h. The product may be purified via sgc or crystallization.

General Scheme II

Preparation of Methylene Linked Compounds



Description of reactions-General Scheme II

In step 1, trifluoroacetic anhydride is dissolved in a suitable inert solvent such as methylene chloride and treated with a benzyl amine at ambient temperature, then stirred for 1-5 h. Methanesulfonic acid (2 eq) is added followed by dibromodimethylhydantoin and the reaction mixture is stirred overnight at rt and subjected to aqueous work up. The product may be purified by chromatography or crystallization.

In step 2, the product of step 1 is dissolved in THF, cooled in a dry ice/acetone bath (-78°C) and treated with methyllithium, then n-BuLi. The dianion is then treated with a THF solution containing the aldehyde (i). The resulting mixture is warmed to rt and stirred for 10 h. The product is purified by chromatography.

In step 3, the alcohol product from step 2 is dissolved in methylene chloride and treated with ten fold excess of triethylsilane followed by a slight excess of boron trifluoride etherate. The resulting mixture is stirred at room temperature for 4h, and purified by chromatography.

In step 4, the product of step 3 is dissolved in a suitable solvent such as dioxane, ethanol, or THF and an alkali metal hydroxide such as lithium hydroxide is

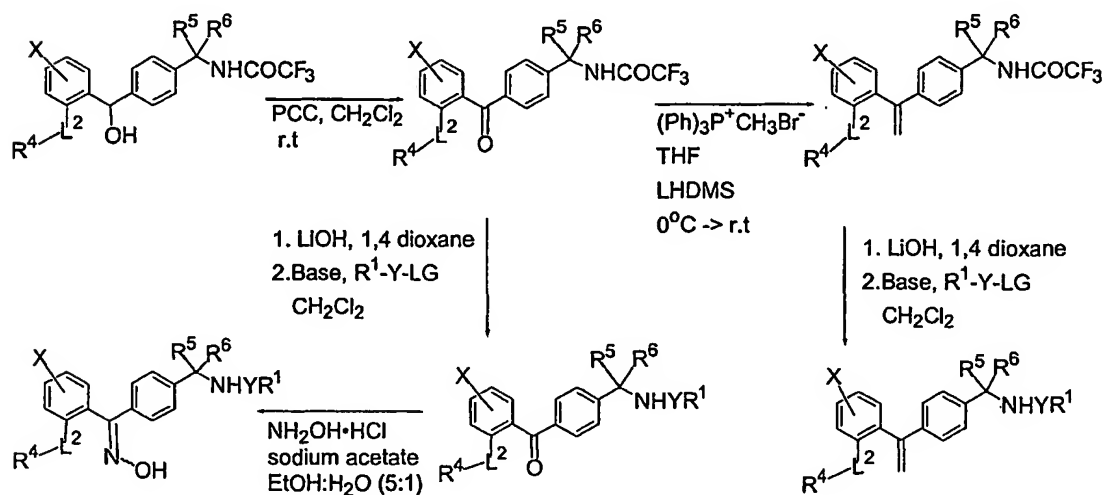
added either as an aqueous solution or as a solid. The reaction mixture is stirred at rt for 0.5-24 h.

In step 5, the product of step 4 is dissolved in a mixture of a suitable inert solvent such as CH_2Cl_2 or dioxane and a tertiary amine base, and a suitable
5 electrophile is added. The reaction mixture is stirred between -78°C and 100°C for 0.5 to 48 h.

In step 6, the product of step 5 is dissolved in a suitable inert solvent such as THF or CH_2Cl_2 and treated with a suitable base such as NaH or triethylamine. An electrophile is added and the reaction mixture is stirred between 0°C and 100°C for 0.5 to 48 h.

The aldehyde (i) used in step 2 was prepared by one of the following two procedures; 1) Regioselective ortho lithiation of a 4-substituted benzaldehyde, and quenching with a substituted phenyl disulfide followed by oxidation with metachloroperoxybenzoic acid to the sulfone. 2) Base promoted displacement of fluoride from an ortho-fluorobenzaldehyde by a thiophenol, phenol, or aniline.

General Scheme III Preparation of Ketone and Olefin Linked Compounds



Description of reactions-General Scheme III

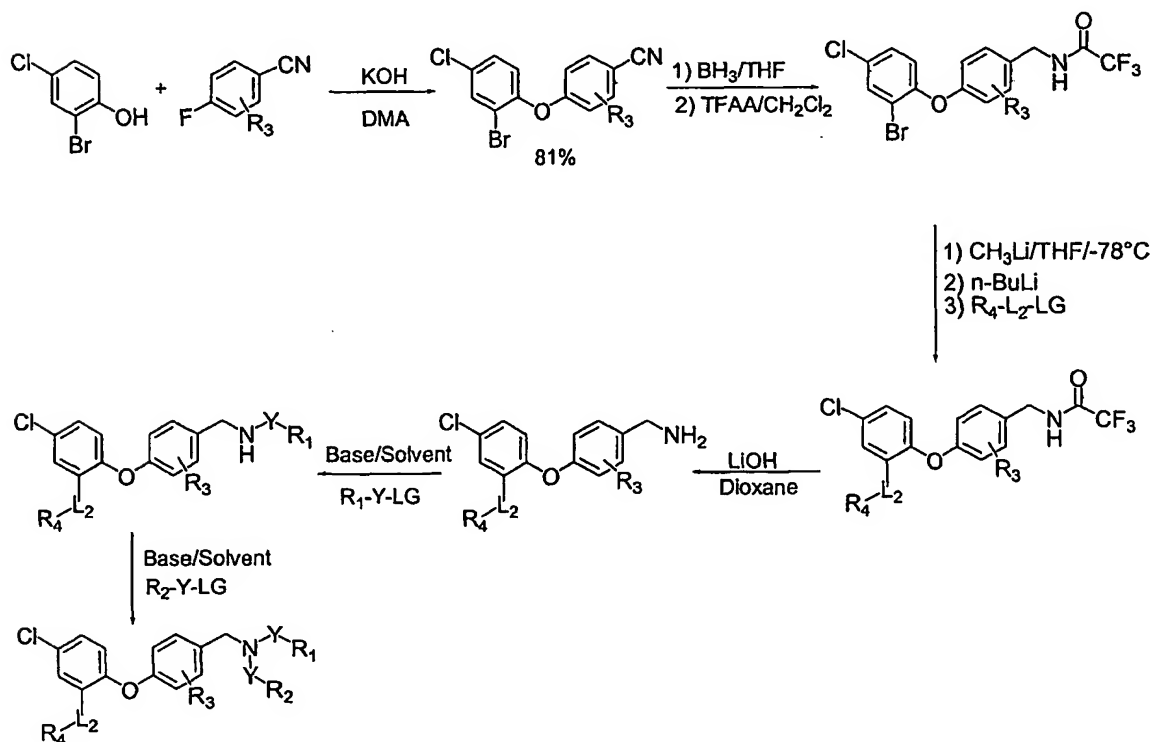
In step 1 the secondary alcohol, the product of Step 2 in Scheme II is oxidized
10 with PCC, in a suitable inert solvent such as CH_2Cl_2 , to the carbonyl by stirring at rt for 18 h. In step 2, the ketone is treated with the ylide obtained by base treatment of dried methyltriphenylphosphonium bromide, providing the exo methylene product. In

- 14 -

step 3 the trifluoroacetamide group can be hydrolyzed with base and reacted with a variety of acylating, sulfonylating, alkylating and other electrophilic reagents.

The ketone product can be treated with hydroxylamine hydrochloride in pyridine and heated at 80°C for 24 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. Upon workup and purification, the oxime is obtained.

General Scheme IV Preparation of Oxygen Linked Compounds



Description of reactions-General Scheme IV

- 5 In step 1, 2-bromo-4-chlorophenol and a 4-fluorobenzonitrile are dissolved in a polar aprotic solvent such as DMA in the presence of a suitable base such as potassium hydroxide. The reaction mixture is heated for 0.5-7 days. Preferred temperatures are greater than 60 °C. The reaction mixture is diluted with a suitable extraction solvent such as diethyl ether and washed with water. The solvents are
- 10 removed and the product is purified via sgc.

- 15 -

In step 2, the product of step 1 is dissolved in a solution of diborane in THF. The reaction is stirred at reflux for 1-24 h then quenched with water and partitioned between EtOAc and aq NaOH. The solvents are evaporated and the product is purified by formation of the HCl salt in diethyl ether.

5 In step 3, the product of step 2 is suspended in CH₂Cl₂ and a suitable base such as triethylamine is added. The reaction mixture is cooled, and TFAA is added. The reaction mixture is stirred from 0.5 to 8 h, then subjected to aqueous workup. The crude product is purified by sgc.

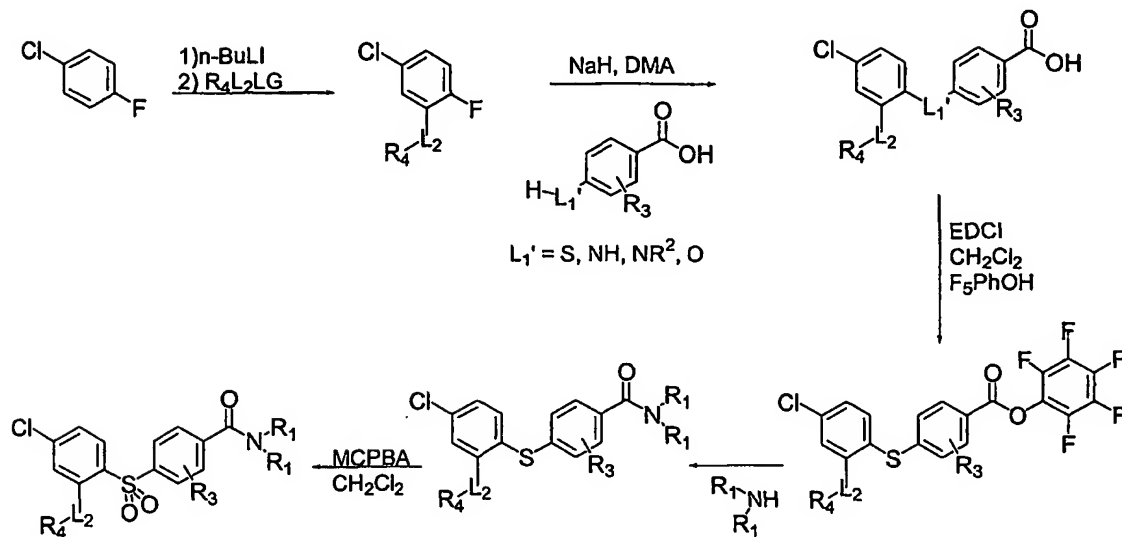
10 In step 4, the product of step 3 is dissolved in THF and treated with methyl lithium, then n-BuLi at -78 °C to form a dianion that is trapped with a suitable electrophile. The reaction mixture is quenched with a suitable proton source such as aq NH₄Cl or phosphate buffer then extracted with EtOAc. The product may be purified via sgc or crystallization.

15 In step 5, the product of step 4 is dissolved in a suitable solvent such as dioxane, ethanol, or THF and an alkali metal hydroxide such as lithium hydroxide is added either as an aqueous solution or as a solid. The reaction mixture is stirred at rt for 0.5-24 h.

20 In step 6, the product of step 5 is dissolved in a mixture of a suitable inert solvent such as CH₂Cl₂ or dioxane and a tertiary amine base, and a suitable electrophile is added. The reaction mixture is stirred between -78°C and 100 °C for 0.5 to 48 h.

In step 7, the product of step 6 is dissolved in a suitable inert solvent such as THF or CH₂Cl₂ and treated with a suitable base such as NaH or triethylamine. An electrophile is added and the reaction mixture is stirred between 0°C and 100°C for 0.5 to 48 h.

General Scheme V
Preparation of Amide Compounds



Description of Reactions-General Scheme V

In step 1, 1-chloro-4-fluorobenzene is dissolved in anhyd THF and treated with
 5 n-BuLi at -78°C to form an anion that is trapped with a suitable electrophile. The product may be purified via sgc or crystallization.

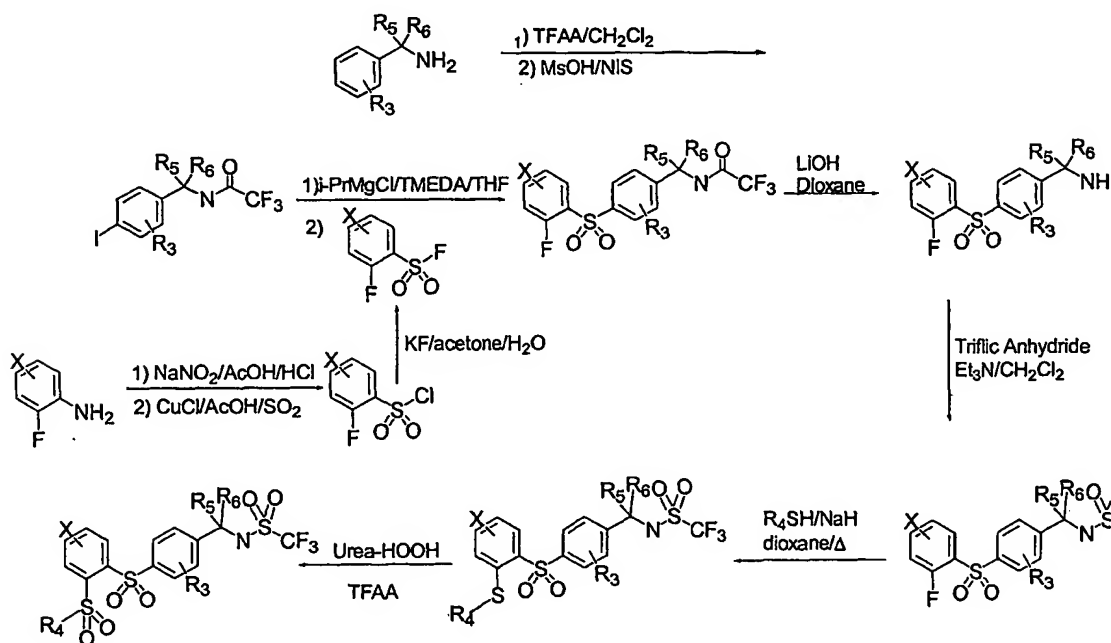
In step 2, the product of step 1 is dissolved in a suitable polar solvent such as acetonitrile or DMA. A benzoic acid containing a nucleophilic moiety such as an OH, NHR, or SH is added, and two or more equivalents of a suitable base such as
 10 potassium hydroxide or sodium hydride is added. The reaction mixture may be stirred for 1-24 h at temperatures ranging between 0°C and 150°C . The reaction mixture is partitioned between water and a suitable solvent such as EtOAc. The product may be purified via sgc or crystallization.

In step 3, the product of step 2 is dissolved in CH_2Cl_2 . Pentafluorophenol and
 15 EDCI are added. The reaction mixture is stirred at rt for 0.5-24 h then partitioned between water and CH_2Cl_2 . The solvents are evaporated. The product may be purified via sgc or crystallization.

In step 4, the product of step 3 is dissolved in a suitable solvent such as CH_2Cl_2 . An amine base such as DIPEA or triethylamine is added, followed by a
 20 primary or secondary amine. The reaction mixture may be stirred for 1-24 h at rt. The reaction mixture is then subjected to aqueous workup and isolation and the product is purified via sgc.

In step 5, if the nucleophilic moiety in step 2 contains oxidizable functionality, the product of step 4 is dissolved in a suitable solvent such as CH_2Cl_2 and MCPBA is added. The reaction mixture may be stirred for 0.5-48 h then partitioned between a suitable solvent such as CH_2Cl_2 or EtOAc and an aqueous base such as Na_2CO_3 . The solvent is evaporated and the product is purified via sgc.

General Scheme VI C-Ring Addition Elimination Chemistry



Description of Reactions-General Scheme VI

In step 1, trifluoroacetic anhydride is dissolved in a suitable inert solvent such as methylene chloride and reacted with a benzyl amine at rt for 1-5 h. Methanesulfonic acid (2 eq) is added followed by N-iodosuccinimide. The reaction mixture is stirred overnight at rt, then subjected to aqueous work up. The crude product is recrystallized from isopropanol and water.

In step 2, CuCl is dissolved in glacial acetic acid. The flask is cooled to 0 °C and SO_2 gas is bubbled in with stirring for 40 min. In a separate flask 2-fluoro-4-chloroaniline is dissolved in glacial acetic acid and concentrated HCl. The resulting

- 18 -

solution is cooled to 0 °C and treated with an aqueous solution of NaNO₂. The reaction mixture is stirred for 30 min at 0 °C and the contents are added to the flask containing the SO₂ solution causing vigorous gas evolution. The reaction is then allowed to warm to rt. The product is isolated by pouring the reaction mixture onto
5 chipped ice, then filtering the resulting solid.

In step 3, the product of step 2 is dissolved in acetone. An aqueous solution of KF (2 eq) is added and the reaction mixture is stirred for 12-24 h at rt. The reaction mixture is extracted with a suitable solvent such as CH₂Cl₂ or Et₂O and the solvent is evaporated to afford the product.

10 In step 4, the product of step 1 is dissolved in THF and TMEDA is added. The flask is placed under N₂ blanket, and cooled to 0 °C. A solution of isopropyl magnesium chloride in THF is added and the reaction mixture is stirred for 1-4 h. The resulting solution is added to a flask containing the product of step 3 that was cooled with an ice-water bath. The reaction mixture is stirred for 1-3 h. The reaction is
15 quenched with aqueous NH₄Cl and extracted with EtOAc. After evaporation of the solvent, the crude product is purified via sgc.

In step 5, the product of step 4 is dissolved in a suitable solvent such as dioxane, ethanol, or THF and an alkali metal hydroxide such as lithium hydroxide is added either as an aqueous solution or as a solid. The reaction mixture is stirred at rt
20 for 0.5-24 h. The product may be purified via sgc or crystallization.

In step 6, the product of step 5 is dissolved in a suitable inert solvent such as CH₂Cl₂ or acetonitrile and a tertiary amine base, and a triflic anhydride is added. The reaction mixture is stirred between -78°C and rt for 0.5 to 48 h. The product may be purified via sgc or crystallization.

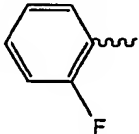
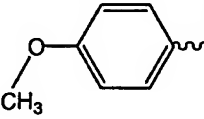
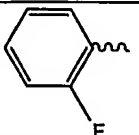
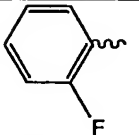
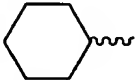
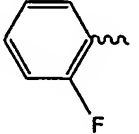
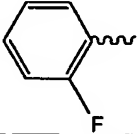
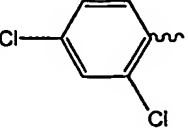
25 In step 7, the product of step 6 is dissolved in a suitable inert solvent such as dioxane and a thiol is added. A base such as sodium hydride, sodium hydroxide, or NaHMDS is added and the reaction mixture is stirred at a suitable temperature between 50 °C and 100 °C for 4-24 h. The reaction mixture is quenched with water and extracted with a suitable solvent. The solvents are evaporated and the crude
30 product is purified via sgc.

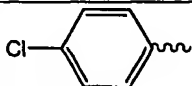

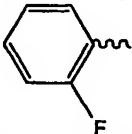
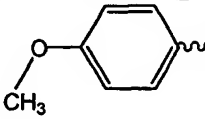
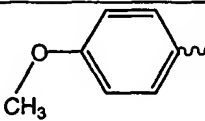
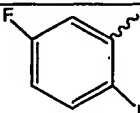
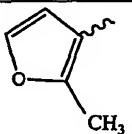
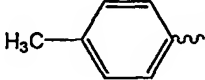
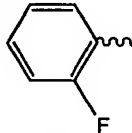
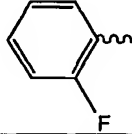
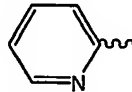
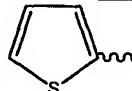
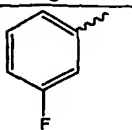
In step 8, the product of step 7 is dissolved in a suitable inert solvent such as CH₂Cl₂. Na₂HPO₄ and urea hydrogen peroxide complex is added, followed by TFAA.

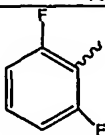
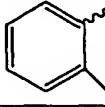
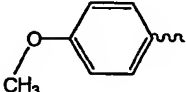

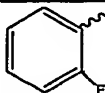
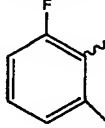
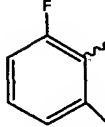
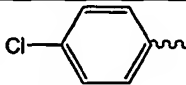
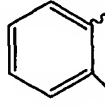
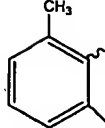
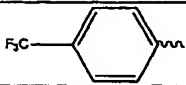
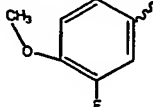
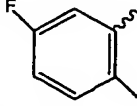
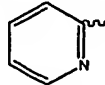
The reaction mixture is refluxed for 4-16 h, then partitioned between water and CH_2Cl_2 . The solvents are evaporated and the crude product is purified via sgc.

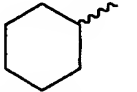
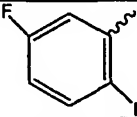
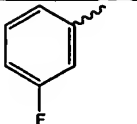
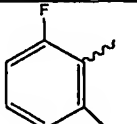
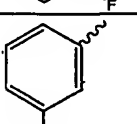
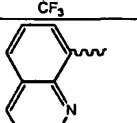
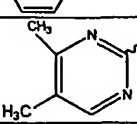
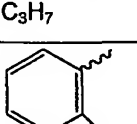
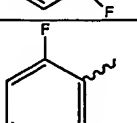
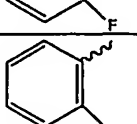
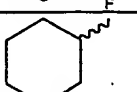
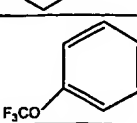
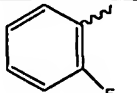
Those skilled in the art will appreciate that similar reactions to those described
 5 in the above schemes may be carried out on other compounds of formula I as long as substituents present would not be susceptible to the reaction conditions described. Starting materials for the above processes are either commercially available, known in the art, or prepared by procedures well known in the art. Exemplary compounds of
 10 formula 1 are set forth below in Table I. CB means covalent bond.

TABLE I

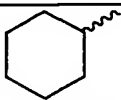
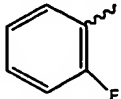
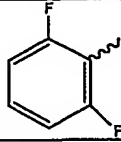
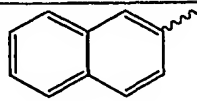
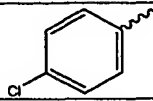
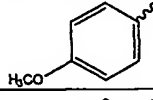
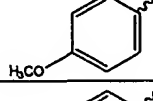
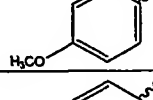
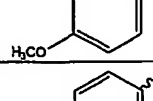
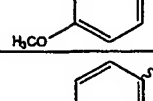
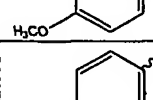
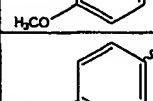
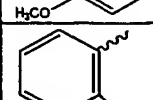
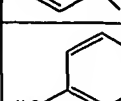
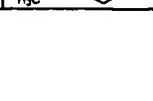
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A	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
B	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
C	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCF ₂ H	SO ₂	CB
D	CH ₃	H	H	t-butoxy	H	CH ₃	SO ₂	CO	OCH ₃	SO ₂	CB
E	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
F	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
G	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	CH ₃	SO ₂	CB
H	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB
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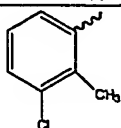
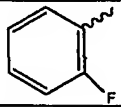
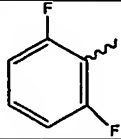
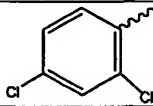
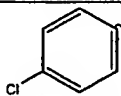
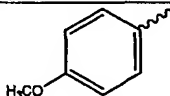
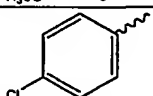
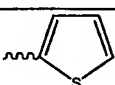
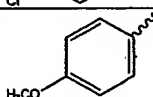
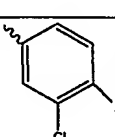
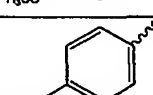
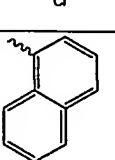
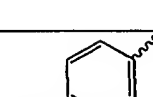
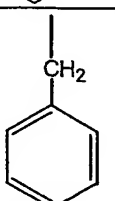
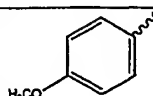
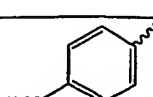
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J	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCF ₃	SO ₂	CB
K	CH ₃	H	H	t-butoxy	H	CH ₃	SO ₂		OCF ₂ H	SO ₂	CB
L	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
M	CH ₃	H	H		H	H	SO ₂	SO ₂	OCH ₃	SO ₂	CB
N	CH ₃	H	H		H	H	CH ₂	SO ₂	OCH ₃	SO ₂	CB
O	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
P	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
Q	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	CH ₃	SO ₂	CB
R	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
S	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
T	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
U	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
V	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB

	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
W	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
X	CF ₃	H	H		CH ₃	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
Y	C ₄ H ₉	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
Z	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
AA	CH ₃	H	H	C ₃ H ₇	H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
AB	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
AC	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
AE	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
AF	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
AG	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
AH	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
AI	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
AK	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AM	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
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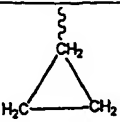
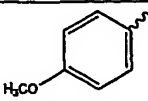
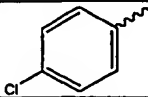
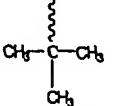
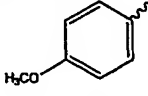
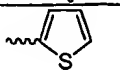
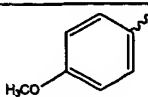
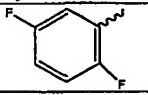
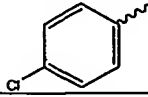
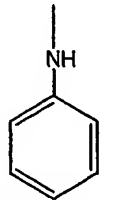
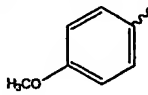
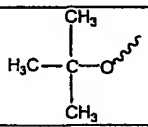
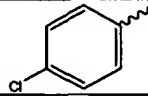
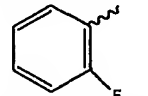
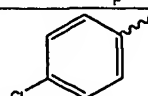
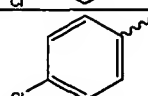
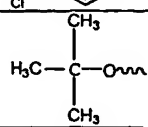
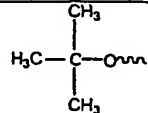
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AR	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AS	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AT	N(CH ₃) ₂	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AU	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AV	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AW	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AX	CH ₃	H	H	C ₃ H ₇	H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
AY	CF ₃	H	H		CH ₃	CH ₃	SO ₂	SO ₂	Cl	O C	CB
AZ	CF ₃	H	H		CH ₃	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
BA	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCF ₃	SO ₂	CB
BB	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCF ₃	SO ₂	CB
BC	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCF ₃	SO ₂	CB
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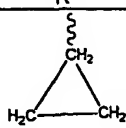
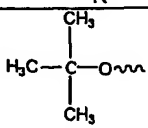
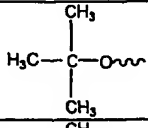
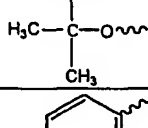
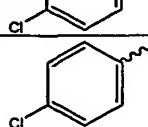
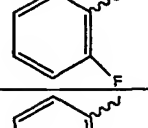
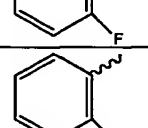
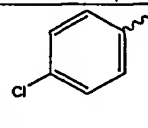
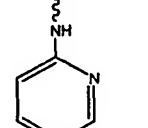
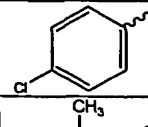
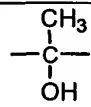
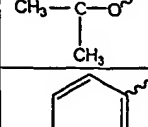
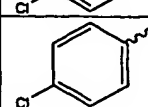


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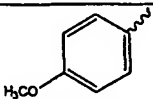
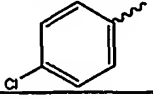
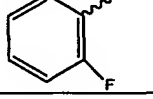
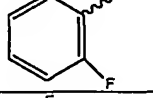
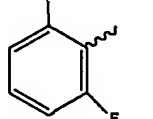
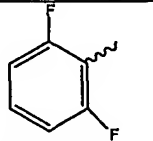
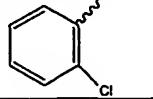
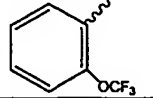
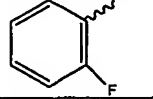
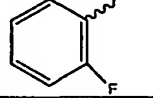
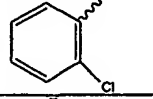
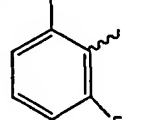
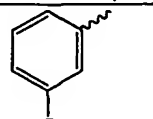
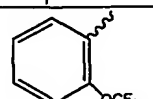
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
BG	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BH	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
BJ	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BN	CF ₃	H	H	C ₃ H ₇	H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
BO	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
BP	NHC ₃ H ₇	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
BR	CF ₃	H	H		CH ₃	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
BS	CH ₃	H	H		CH ₃	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BT	CH ₃	CH ₃	H		CH ₃	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BU	CH ₃	H	H		H	H	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BV	CH ₃	CH ₃	H		H	H	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BW	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
BX	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BY	CH ₃	CH ₃	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
BZ	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	CH ₃	SO ₂	CB
CA	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	CH ₃	SO ₂	CB

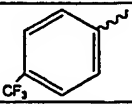
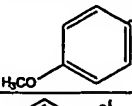
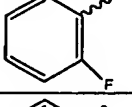
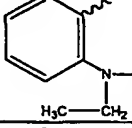
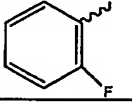
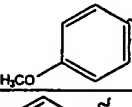
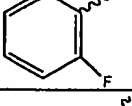
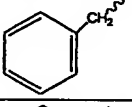
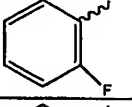
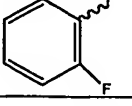
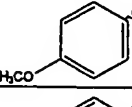
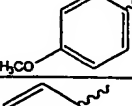
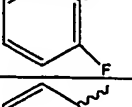
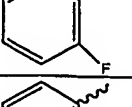
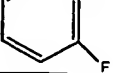
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
CB	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	CH ₃	SO ₂	CB
CC	CF ₃	H	H	C ₃ H ₇	H	CH ₃	SO ₂	SO ₂	Cl	C=O	CB
CD	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
CE	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
CF	-CH(CH ₃) ₂	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CG	NH ₂	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CH	C ₄ H ₉	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CI	-CHCF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CJ		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CK		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CL		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CM		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
CN	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB

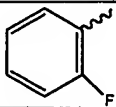
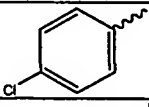
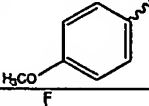
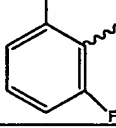
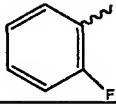

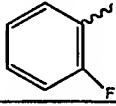

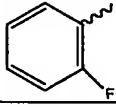

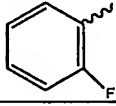

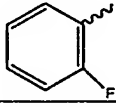

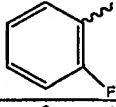

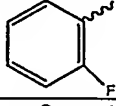

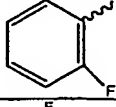

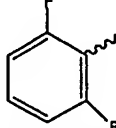
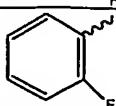
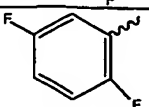
- 25 -

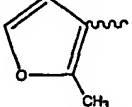

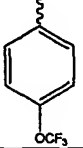
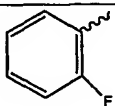
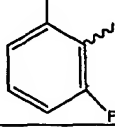
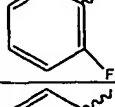
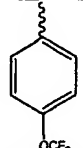
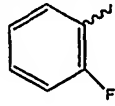
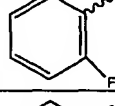
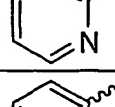
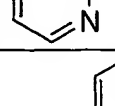
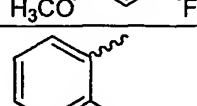
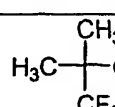
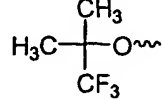
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
CO		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
CP	C ₃ H ₇	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
CQ		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
CR		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
CS	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	C=O	CB
CT	NH-(CH ₂) ₂ -CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
CU		H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB
CV	CF ₃	H	H		H	CH ₃	SO ₂	C=O	OH	C=O	CB
CW	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OH	SO ₂	CB
CX	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OH	SO ₂	CB
CZ	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCF ₂ H	C=O	CB
DA	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCF ₂ H	SO ₂	CB
DC	CF ₃	H	H		H	CH ₃	SO ₂	C=O	OCH ₃	SO ₂	CB
DD	CF ₃	H	H		H	CH ₃	SO ₂	C=O	OCH ₃	C=O	CB

	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
DE		H	H		H	CH ₃	SO ₂	C=O	OCH ₃	C=O	CB
DF	CH ₃	H	H		H	CH ₃	SO ₂	C=O	Cl	SO ₂	CB
DG	CF ₃	H	H		H	CH ₃	SO ₂	C=O	Cl	SO ₂	CB
DH	CH ₃	H	H		H	CH ₃	SO ₂	CH ₂	Cl	SO ₂	CB
DI	CH ₃	H	H		H	CH ₃	SO ₂	C=O	Cl	SO ₂	CB
DJ	CH ₃	H	H		H	CH ₃	SO ₂	CH ₂	Cl	SO ₂	CB
DK	CH ₃	H	H		H	CH ₃	SO ₂	C=O	Cl	SO ₂	CB
DL	CH ₃	H	H		H	CH ₃	SO ₂	C=CH ₂	Cl	SO ₂	CB
DM	CF ₃	H	H		H	CH ₃	SO ₂		Cl	C=O	CB
DN	CF ₃	H	H		H	CH ₃	SO ₂	C=O	Cl	C=O	CB
DP	CF ₃	CH ₃	H		H	CH ₃	SO ₂	C=CH ₂	Cl	C=O	CB
DQ	CH ₃	H	H		CH ₃	CH ₃	SO ₂	C=O	Cl	SO ₂	CB
DR	CH ₃	H	H		H	CH ₃	SO ₂	NH	Cl	SO ₂	CB
DS	CF ₃	H	H		H	CH ₃	SO ₂	O	Cl	C=O	CB

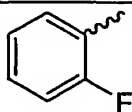
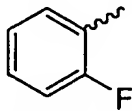
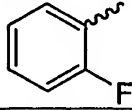
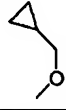
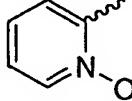
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
DU	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCH ₃	SO ₂	CB
DV	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	Cl	SO ₂	CB
DW	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB
DX	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB
DY	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB
DZ	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB
EA	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB
EC	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	CF ₃	SO ₂	CB
ED	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	C=O	CB
EE	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
EG	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
EH	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
EI	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
EJ	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB

	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
EK	CF ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
EL	CH ₃	H	H		H	H	CH ₂	SO ₂	OCH ₃	SO ₂	CB
EN	CF ₃	H	H		CH ₃	CH ₃	CH ₂	SO ₂	OCF ₃	C=O	CB
EP	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
EU	CH ₃	H	H		H	CH ₃	C=O	SO ₂	OCF ₃	SO ₂	CB
EV	CF ₃	H	H		H	CH ₃	C=O	SO ₂	OCH ₃	SO ₂	CB
EW	CF ₃	H	H		H	CH ₃	C=O	O	H	C=O	CB
EX	CF ₃	H	H		H	CH ₃	C=O	O	H	C=O	CB
EY	CF ₃	H	H		H	CH ₃	C=O	O	Cl	C=O	CB
EZ	CH ₃	H	H		H	CH ₃	C=O	SO ₂	OCF ₃	C=O	CB
FA	CF ₃	H	H		H	CH ₃	C=O	NHSO ₂	H	C=O	CB
FB	CF ₃	H	H		H	CH ₃	C=O	NHCO	H	C=O	CB
FC	CF ₃	H	H		H	CH ₃	C=CH ₂	SO ₂	OCF ₃	C=O	CB
FD	CH ₃	H	H		H	CH ₃	C=CH ₂	SO ₂	OCF ₃	SO ₂	CB
FE	CF ₃	H	H		H	CH ₃	C=O	SO ₂	OCF ₃	SO ₂	CB

	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
FF	CH ₃	H	H		H	CH ₃	C=NO H	SO ₂	OCF ₃	SO ₂	CB
FG	CH ₃	H	H		H	CH ₃	C(CH ₃) ₂	SO ₂	Cl	SO ₂	CB
FH	CF ₃	H	H		H	H	C=O	SO ₂	OCH ₃	C=O	CB
FI	CH ₃	H	H		H	H	O	SO ₂	Cl	SO ₂	CB
FJ	*R ¹ , Y, Z and R ² combine to form morpholinyl	*	H		-		S	SO ₂	Cl	*	*
FK	H	CH ₃	H		-		S=O	SO ₂	Cl	CB	CB
FL	H	CH ₃	H		-		SO ₂	SO ₂	Cl	CB	CB
FM	*R ¹ , Y, Z and R ² combine to form morpholinyl	*	H		-		SO ₂	SO ₂	Cl	*	*
FN	CH ₃	CH ₃	H		-		S	SO ₂	Cl	CB	CB
FO	H	H	H		-		S	SO ₂	Cl	CB	CB
FP	CH ₃	CH ₃	H		-		SO ₂	SO ₂	Cl	CB	CB
FQ	H	H	H		-		SO ₂	SO ₂	Cl	CB	CB
FR	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	SO ₂	CB
FS	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	SO ₂	CB
FT	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	SO ₂	CB

	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
FU	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	C=O	CB
FV	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	SO ₂	CB
FW	CH ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	SO ₂	CB
FX	CF ₃	H	H	~CH ₃	H	CH ₃	SO ₂	SO ₂	H	C=O	CB
FY	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	SO ₂	CB
FZ	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	H	SO ₂	CB
GA	CH ₃	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	C=O	CB
GD		H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
GF	NHC ₂ H ₅	H	H		H	CH ₃	CH ₂	SO ₂	OCF ₃	SO ₂	CB
GG	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
GH	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	CF ₃	SO ₂	CB
GI	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	Cl	SO ₂	CB
GJ	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	SO ₂	CB
GK	CF ₃	H	H		H	CH ₃	SO ₂	C=O	OCH ₃	SO ₂	CB

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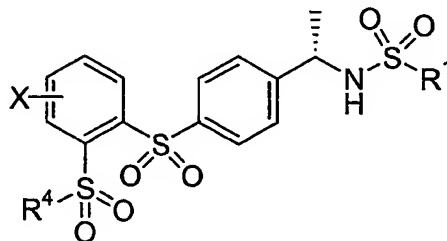
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	L ¹	L ²	X	Y	Z
GL	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OH	SO ₂	CB
GM	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH(CH ₃) ₂	SO ₂	CB
GN	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂		SO ₂	CB
GO	CF ₃	H	H		H	CH ₃	SO ₂	SO ₂	OCH ₃	C=O	CB

CB is a covalent bond

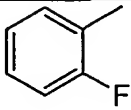
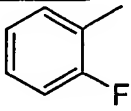
- means that the substituent is not present

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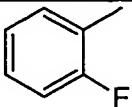
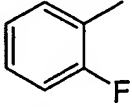
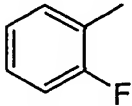
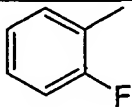
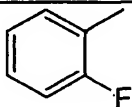
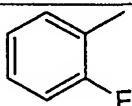
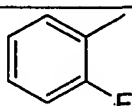
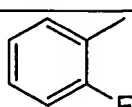
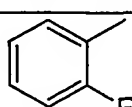
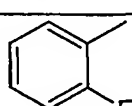
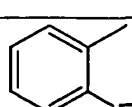
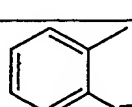
In a preferred embodiment, there are disclosed compounds of the formula



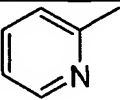
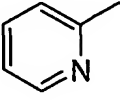

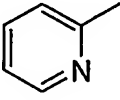

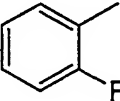

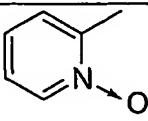
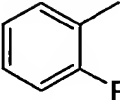
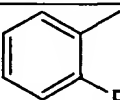
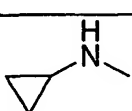
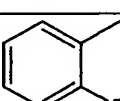
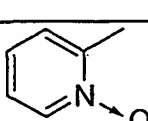
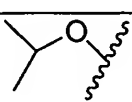
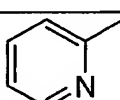
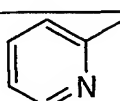
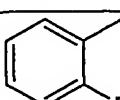
- 10 a prodrug thereof, or a pharmaceutically acceptable salt of the compound or of said prodrug; wherein X, R¹ and R⁴ are as shown in the table below:

Example	X	R ¹	R ⁴
A	OCH ₃	CH ₃	
C	OCF ₂ H	CH ₃	

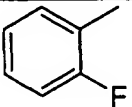
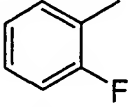
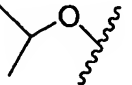
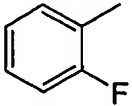
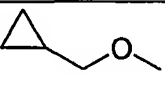
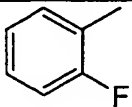
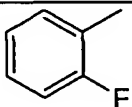
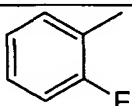
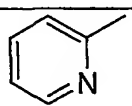

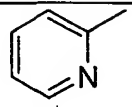
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Example	X	R ¹	R ⁴
G	CH ₃	CH ₃	
L	Cl	CH ₃	
R	CF ₃	CF ₃	
S	Cl	CF ₃	
AB	CF ₃	CH ₃	
AT	Cl	N(CH ₃) ₂	
BA	OCF ₃	CH ₃	
BD	OCF ₃	CF ₃	
BZ	CH ₃	CF ₃	
CD	Cl	CH ₃	
FS	H	CH ₃	
FY	H	CF ₃	

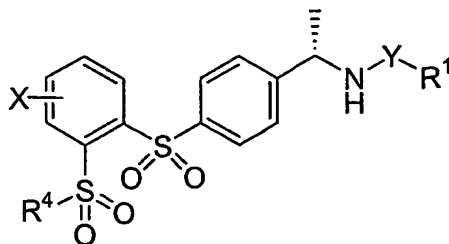
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Example	X	R ¹	R ⁴
GG	Cl	CF ₃	
GH	CF ₃	CF ₃	
XXIX		CF ₃	
XXX		CF ₃	
XXXI		CF ₃	
XXXII	CN	CF ₃	
XXXIII	NH ₂	CF ₃	
XXXIV		CF ₃	
XXXVI	Cl	CF ₃	
XXXVII		CF ₃	
XXXVIII	CN	CF ₃	
XXXIX	-CONH ₂	CF ₃	

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Example	X	R ¹	R ⁴
XXXXX	-OCH ₃	CF ₃	
XXXXXI	-OH	CF ₃	
XXXXXII		CF ₃	
XXXXXIII		CF ₃	
XXXXXIV	H ₃ C-CH ₂ -O-	CF ₃	
XXXXXV	H ₃ C-O-CH ₂ -CH ₂ -O-	CF ₃	
XXXXXV	OCH ₃	CF ₃	
XXXXXXVI		CH ₃	


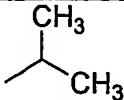
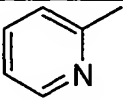

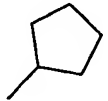
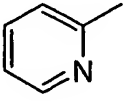

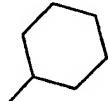
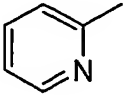


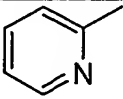
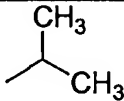
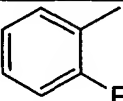
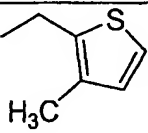
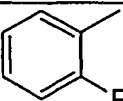
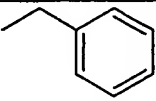
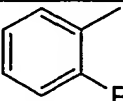
In another preferred embodiment, there are disclosed compounds of the formula



5

a prodrug thereof, or a pharmaceutically acceptable salt of the compound or of said prodrug; wherein X, Y-R¹ and R⁴ are as shown in the table below:

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Example	X	Y-R ¹	R ⁴
XXXXVI			
XXXXVII			
XXXXVIII			
XXXXIX			
XXXXXI	-OCH ₃		
XXXXXII	-OCH ₃		
XXXXXIII	-OCH ₃		

Compound A : ¹H NMR (300 MHz, CDCl₃) 1.54 (d, J = 6.9Hz 3H), 2.67 (s, 3H), 4.72 (q, J = 5Hz 1H), 4.86 (br. d, J = 5Hz, 1H, NH), 7.08-8.42 (m, 11H).

- 5 Compound C : ¹H NMR (400 MHz, CDCl₃) 1.51 (d, J = 7.2Hz 3H), 2.67 (s, 3H), 4.702 (q, J = 6.8Hz 1H), 5.05 (br. d, J = 6.4Hz, 1H, NH), 6.71 (t, J = 71.6 Hz, CF₂H) 7.07-8.47 (m, 11H).

- 10 Compound G : ¹H NMR (300 MHz, CDCl₃) 8.43-8.41 (m, 1H), 8.36 (d, 8Hz, 1H), 8.28-8.22 (m, 1H), 7.96-7.92 (m, 2H), 7.69-7.60 (m, 2H), 7.52-7.47 (m, 2H), 7.43-7.37 (m, 1H), 7.13-7.06 (m, 1H), 4.76-4.70 (m, 2H), 2.68 (s, 3H), 2.59 (s, 3H), 1.41 (d, 7 Hz, 3H).

- 15 Compound L : ¹H NMR (300 MHz, CDCl₃) 8.61-5.97 (m, 2H), 8.40 (d, 8 Hz, 1H), 8.24-8.21 (m, 1H), 7.96 (d, 8 Hz, 2H), 7.86-7.83 (m, 1H), 7.70-7.63 (m, 1H), 7.52 (d, 8

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Hz, 2H), 7.46-7.40 (m, 1H), 7.18-7.12 (m, 1H), 4.80-4.70 (m, 1H), 2.71 (s, 3H), 1.56 (d, 7Hz, 3H).

5 Compound R : ^1H NMR (300 MHz, CDCl_3) 8.89-8.87 (m, 1H), 8.58 (d, 8Hz, 1H), 8.32-8.25 (m, 1H), 8.15-8.11 (m, 1H), 8.03-7.98 (m, 2H), 7.71-7.63 (m, 1H), 7.52-7.48 (m, 2H), 7.47-7.41 (m, 1H), 7.16-7.09 (m, 1H), 5.62 (d, 8 Hz, 1H), 4.90-4.80 (m, 1H), 1.63 (d, 7 Hz, 3H).

10 Compound S : ^1H NMR (300 MHz, CDCl_3) 8.61-8.59 (m, 1H), 8.39 (d, 8 Hz, 1H), 8.29-8.24 (m, 1H), 7.99 (d, 8 Hz, 2H), 7.86-7.82 (m, 1H), 7.67-7.62 (m, 1H), 7.49 (d, 8Hz, 1H), 7.46-7.40 (m, 1H), 7.16-7.10 (m, 1H), 4.89-4.84 (m, 1H), 1.65 (d, 6 Hz, 1H).

15 Compound AB : ^1H NMR (300 MHz, CDCl_3) 8.88-8.86 (m, 1H), 8.62-8.59 (m, 1H), 8.30-8.29 (m, 1H), 8.15-8.11 (m, 1H), 8.00-7.96 (m, 2H), 7.71-7.63 (m, 1H), 7.56-7.52 (m, 2H), 7.47-7.41 (m, 1H), 7.16-7.09 (m, 1H), 4.99-4.84 (m, 1H), 4.80-4.70 (m, 1H), 2.71 (s, 3H), 1.54 (d, 7Hz, 3H).

20 Compound AT : ^1H NMR (300 MHz, CDCl_3) 8.51 (br s 1H), 8.39 (d, 8 Hz, 2H), 7.99 (d, 8 Hz, 2H), 7.86-7.83 (m, 1H), 7.61-7.50 (m, 1H), 7.49 (d, 8 Hz), 7.05-6.99 (m, 1H), 4.70-4.50 (m, 2H), 2.83 (s, 3H), 2.57 (s, 3H), 1.50 (d, 7 Hz, 3H).

Compound BA : ^1H NMR (300 MHz, CDCl_3) 1.54 (d, $J = 6.9$ Hz 3H), 2.7 (s, 3H), 4.72 (q, $J = 5.5$ Hz 1H), 5.05 (br. d, $J = 5$ Hz, 1H, NH), 7.1 -8.55 (m, 11H).

25 Compound BD : ^1H NMR (300 MHz, CDCl_3) 8.51 (d, 9 Hz, 1H), 8.47-8.45 (m, 1H), 8.01-7.97 (m, 2H), 7.71-7.63 (m, 2H), 7.52-7.41 (m, 3H), 7.17-7.10 (m, 1H), 5.51 (d, 8 Hz, 1H), 4.90-4.80 (m, 1H), 1.64 (d, 7 Hz, 3H).

30 Compound BZ : ^1H NMR (300 MHz, CDCl_3) 8.43 (br s, 1H), 8.32 (d, 8 Hz, 1H), 8.28-8.22 (m, 1H), 7.94 (d, 8 Hz, 2H), 7.68-7.58 (m, 2H), 7.47-7.37 (m, 3H), 7.12-7.06 (m, 1H), 5.72 (d, 8 Hz, 1H), 4.86-4.70 (m, 1H), 2.59 (s, 3H), 1.60 (d, 7 Hz, 3H).

35 Compound CD : ^1H NMR (300 MHz, CDCl_3): 8.82-8.78 (m, 1H), 8.23 (d, 7 Hz, 2H), 8.21-8.07 (m, 1H), 7.81-7.77 (m, 2H), 7.63-7.57 (m, 1H), 7.55 (d, 7 Hz, 2H), 7.40-7.32 (m, 1H), 7.20-7.16 (m, 1H), 4.8-4.7 (m, 2H), 2.67 (s, 3H), 1.55 (d, 7 Hz, 2H).

40 Compound FS : ^1H NMR (300 MHz, CDCl_3) 8.66-8.62 (m, 1H), 8.51-8.47 (m, 1H), 8.29-8.24 (m, 1H), 7.99-7.95 (m, 2H), 7.93-7.89 (m, 2H), 7.67-7.53 (m, 1H), 7.50-7.44 (m, 2H), 7.42-7.39 (m, 1H), 7.13-7.07 (m, 1H), 4.78-4.73 (m, 1H), 4.61-4.59 (m, 1H), 2.70 (s, 3H), 1.56 (d, 7 Hz, 3H).

45 Compound FY : ^1H NMR (300 MHz, CDCl_3) 8.66-8.63 (m, 1H), 8.49-8.46 (m, 1H), 8.28-8.25 (m, 1H), 8.01 (d, 8 Hz, 2H), 7.93-7.89 (m, 2H), 7.65-7.58 (m, 1H), 7.56 (d, 8 Hz, 2H), 7.47-7.41 (m, 1H), 7.13-7.07 (m, 1H), 5.18 (d, 6 Hz, 1H), 4.90-4.80 (m, 1H), 1.66 (d, 7 Hz, 3H).

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Compound GG : ^1H NMR (300 MHz, CDCl_3): 8.88 (d, 1.2 Hz, 1H), 8.51-8.56 (m, 2H), 8.31 (dd, 8 Hz, 1H, 1H), 8.18 (dd, 8 Hz, 1 Hz, 1H), 8.08-7.96 (m, 3H), 7.62-7.48 (m, 3H), 5.51 (d, 9 Hz, 1H), 4.90-4.70 (m, 1H), 1.62 (d, 7 Hz, 3H).

5 Compound GH : ^1H NMR (300 MHz, CDCl_3): 8.63 (d, 2 Hz), 8.58-8.55 (m, 1H), 8.34-8.28 (m, 2H), 8.07-7.98 (m, 3H), 8.35 (dd, 8 Hz, 2 Hz, 1H), 7.55-7.46 (m, 3H), 5.34 (d, 8 Hz, 1H), 4.9-4.8 (m, 1H), 1.64 (d, 6 Hz, 3H).

10 Compound GQ/XXIX, : ^1H NMR (300 MHz, CDCl_3): δ 8.56-8.52 (m, 1H), 8.32-8.21 (m, 3H), 8.02-7.92 (m, 4H), 5.42 (d, 9 Hz, 1H), 8.02-7.92 (m, 4H), 5.42 (d, 1H, 9 Hz), 4.84-4.78 (m, 1H), 2.16-2.06 (m, 1H), 1.60 (d, 7Hz, 3H), 1.20-1.17 (m, 2H), 0.97-0.89 (m, 1H).

15 Compound GR/XXX, : ^1H NMR (300 MHz, CDCl_3): δ 8.33-8.22 (m, 3H), 8.00-7.94 (m, 2H), 7.66-7.58 (m, 1H), 7.53-7.37 (m, 4H), 7.16-7.05 (m, 1H), 5.160 (d, 9 Hz, 1H), 4.88-4.83 (m, 1H), 2.17-2.06 (m, 1H), 1.65 (d, 7 Hz, 3H), 1.28-1.20 (m, 2H), 0.97-0.90 (m, 2H).

20 Compound GS/XXXI, : ^1H NMR (300 MHz, CDCl_3): δ 8.38-8.29 (m, 2H), 8.17 (d, 8 Hz, 1H), 8.07-8.02 (m, 1H), 7.91-7.85 (m, 2H), 7.56-7.36 (m, 5H), 6.11 (d, 8 Hz, 1H), 4.84-4.78 (m, 1H), 2.12-2.01 (m, 1H), 1.57 (d, 7Hz, 3H), 1.21-1.12 (m, 2H), 0.92-0.86 (m, 2H).

25 Compound GW/XXXVI, : ^1H NMR (300 MHz, CDCl_3): δ 10.19 (d, 7.8 Hz, 1H), 8.27-8.42 (m, 4H), 8.13 (dd, 7.8 Hz, 2.1 Hz, 1H), 7.93 (d, 8.4 Hz, 2H), 7.78-7.63 (m, 2H), 7.59 (d, 8.4 Hz, 2H), 4.80 (m, 1H), 1.44 (d, 6.9 Hz, 3H).

30 Compound HO/XXXXXV, : ^1H NMR (300 MHz, CDCl_3): δ 8.56 (d, 3.9 Hz, 1H), 8.31-8.22 (m, 2H), 8.124 (d, 2.7 Hz, 1H), 8.05-7.95 (m, 1H), 7.92 (d, 8.4 Hz, 2H), .750-7.45 (m, 1H), 7.92 (d, 8.4 Hz, 2H), 7.27-7.23 (m, 2H), 5.8 (d, NH, 1H), 4.85-4.75 (m, 1H), 3.99 (s, 3H), 1.58 (d, 7.2 Hz, 3H).

35 Compound HP/XXXXXVI, : ^1H NMR (300 MHz, CDCl_3): δ 8.56-8.52 (m, 1H), 8.31-8.23 (m, 3H), 8.02-7.90 (M, 4H), 4.87-4.78 (d, 7 Hz, 1H), 4.69 (m, 1 H), 2.66 (s, 3H), 2.16-2.06 (m, 1H), 1.51 (d, 7 Hz, 3H), 1.27 -1.17 (m, 2H), 0.96-0.90 (m, 2H).

The compounds of the present invention exhibit anti-inflammatory and/or immunomodulatory activity and are useful in the treatment of various medical conditions including, e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, nephritis, psoriasis, allergy, inflammatory disorders of the lungs and gastrointestinal tract such as Crohn's disease, and respiratory tract disorders such as reversible airway obstruction, asthma, chronic obstructive pulmonary disease (COPD)

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and bronchitis. This utility is manifested as demonstrated by activity in the following assay.

Potential cannabinoid receptor ligands were screened for the ability to compete with [³H] CP-55,940 for binding to recombinant cannabinoid receptors. Test
5 compounds were serially diluted in Diluent Buffer (50 mM Tris pH 7.1, 1 mM EDTA, 3 mM MgCl₂, 0.1% BSA, 10% DMSO, 0.36% methyl cellulose (Sigma M-6385)) from stocks prepared in 100% DMSO. Aliquots (10 ul) were transferred into 96-well microtiter plates. Membrane preparations of recombinant human cannabinoid CB2 receptor (Receptor Biology #RB-HCB2) or recombinant human cannabinoid CB1
10 receptor (Receptor Biology #RB-HCB1) were diluted to 0.3 mg/ml in Binding Buffer (50 mM Tris pH 7.2, 1 mM EDTA, 3 mM MgCl₂, 0.1% BSA). Aliquots (50 ul) were added to each well of the microtiter plate. The binding reactions were initiated by addition of [³H] CP-55,940 (New England Nuclear # NET 1051; specific activity =180 Ci/mmol) to each well of the microtiter plate. Each 100 ul reaction mixture contained
15 0.48 nM [³H] CP-55,940, 15 ug membrane protein in binding buffer containing 1% DMSO and 0.036 % methyl cellulose. Following incubation for 2 hours at room temperature, the reactions were filtered through 0.5% polyethylenimine-coated GF/C filter plates (UniFilter-96, Packard) with a TomTec Mark 3U Harvester (Hamden, CT). The filter plate was washed 5 times with binding buffer, rotated 180°, then re-washed
20 5 times with binding buffer. Bound radioactivity was quantitated following addition of 30 ul of Packard Microscint 20 scintillant in a Packard TopCount NXT microplate scintillation counter. Non-linear regression analysis of the resulting data was performed using Prism 2.0b (GraphPad, San Diego, CA).

Cannabinoid receptor ligands according to the present invention have anti-
25 inflammatory activity and/or immunomodulatory activity and are useful in the treatment of various medical conditions including, e.g., cutaneous T cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis,
30 psoriasis, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, Crohn's disease, inflammatory bowel disease, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) or

bronchitis. It is contemplated that a compound of this invention may be useful in treating more than one of the diseases listed.

Additionally, a compound of the present invention may be co-administered or used in combination with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, azathioprine, leflunomide, pencillinamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. They may also be co-administered with or used in combination with NSAIDs such as piroxicam, naproxen, indomethacin, ibuprofen and the like; COX-2 selective inhibitors such as Vioxx® and Celebrex®; COX-1 inhibitors such as Feldene; immunosuppressives such as steroids, cyclosporine, Tacrolimus, rapamycin and the like; biological response modifiers (BRMs) such as Enbrel, Remicade, IL-1 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, TACE inhibitors, chemokine receptor antagonists, Thalidomide and other small molecule inhibitors of pro-inflammatory cytokine production. Other drugs that the compounds of the invention may be co-administered or used in combination with include Anaprox, Arava, Arthrotec, Azulfidine, Aspirin, Cataflam, Celestone Soluspan, Clinoril, Cortone Acetate, Cuprimine, Daypro, Decadron, Depen, Depo-Medrol, Disalcid, Dolobid, Naprosyn, Gengraf, Hydrocortone, Imuran, Indocin, Lodine, Motrin, Myochrysine, Nalfon, Naprelan, Neoral, Orudis, Oruvail, Pediapred, Plaquenil, Prelone, Relafen, Solu-Medrol, Tolectin, Trilisate and Volataren. These include any formulation of the abovenamed drugs.

For the treatment of multiple sclerosis, the compounds of the invention may be co-administered or used in combination with Avonex, Betaseron and Copaxone.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of the other agent.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I of this invention and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form known to those skilled in the art. Pharmaceutical compositions containing the compounds of formula I can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such

pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like. All routes of administration are contemplated including, but not limited to, parenteral, transdermal, subcutaneous, intramuscular, sublingual, inhalation, rectal and topical.

Thus, appropriate unit forms of administration include oral forms such as tablets, capsules, powders, cachets, granules and solutions or suspensions, sublingual and buccal forms of administration, aerosols, implants, subcutaneous, intramuscular, intravenous, intranasal, intraocular or rectal forms of administration.

When a solid composition is prepared in the form of tablets, e.g., a wetting agent such as sodium lauryl sulfate can be added to micronized or non-micronized compounds of formula I and mixed with a pharmaceutical vehicle such as silica, gelatin starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, various polymers, or other appropriate substances.

Tablets can be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously or at predetermined intervals, e.g., by using ionic resins and the like.

A preparation in the form of gelatin capsules may be obtained, e.g., by mixing the active principle with a diluent, such as a glycol or a glycerol ester, and incorporating the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir can contain the active principle together, e.g., with a sweetener, methylparaben and propylparaben as antiseptics, flavoring agents and an appropriate color.

Water-dispersible powders or granules can contain the active principle mixed, e.g., with dispersants, wetting agents or suspending agents, such as polyvinylpyrrolidone, as well as with sweeteners and/or other flavoring agents.

Rectal administration may be provided by using suppositories which may be prepared, e.g., with binders melting at the rectal temperature, for example cocoa butter or polyethylene glycols.

Parenteral, intranasal or intraocular administration may be provided by using, e.g., aqueous suspensions, isotonic saline solutions or sterile and injectable solutions containing pharmacologically compatible dispersants and/or solubilizers, for example, propylene glycol or polyethylene glycol.

Thus, to prepare an aqueous solution for intravenous injection, it is possible to use a co-solvent, e.g., an alcohol such as ethanol or a glycol such as polyethylene glycol or propylene glycol, and a hydrophilic surfactant such as Tween® 80. An oily solution injectable intramuscularly can be prepared, e.g., by solubilizing the active
5 principle with a triglyceride or a glycerol ester.

Topical administration can be provided by using, e.g., creams, ointments or gels.

Transdermal administration can be provided by using patches in the form of a multilaminate, or with a reservoir, containing the active principle and an appropriate
10 solvent.

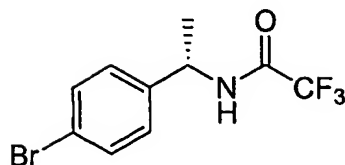
Administration by inhalation can be provided by using, e.g., an aerosol containing sorbitan trioleate or oleic acid, for example, together with trichlorofluoromethane, dichlorofluoromethane, dichlorotetrafluoroethane or any other biologically compatible propellant gas; it is also possible to use a system containing
15 the active principle, by itself or associated with an excipient, in powder form.

The active principle can also be formulated as microcapsules or microspheres, e.g., liposomes, optionally with one or more carriers or additives.

Implants are among the prolonged release forms which can be used in the case of chronic treatments. They can be prepared in the form of an oily suspension or
20 in the form of a suspension of microspheres in an isotonic medium.

The daily dose of a compound of formula I for treatment of a disease or condition cited above is about 0.001 to about 100 mg/kg of body weight per day, preferably about 0.001 to about 10 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 0.1 to about 700 mg of drug per day, given in a
25 single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

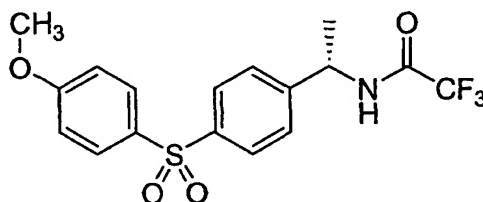
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EXAMPLE I

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Compound 1

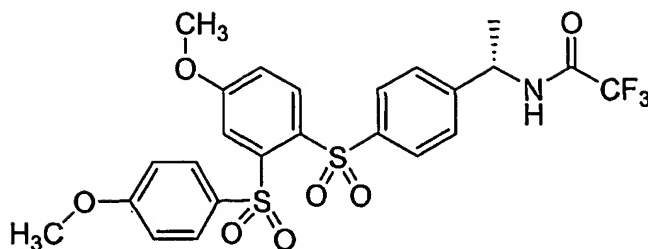
Compound 1. TFAA (67 mL, 0.474 mol) was dissolved in CH_2Cl_2 (300 mL) and cooled in an ice water bath. A solution of (S)- α -methylbenzylamine (56.4 g, 0.465 mol) dissolved in CH_2Cl_2 (100 mL) was added and the ice bath was removed. The
10 reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled in an ice bath and MsOH (80 mL, 1.23 mol) was added followed by DBDMH (65 g, 0.227 mol). The reaction mixture was left stirring overnight at rt then quenched with 1M aq NaHSO_3 . The organic layer was washed with water and brine, dried with MgSO_4 , and concentrated to give 130 g of white solid. The crude product was recrystallized from
15 Et_2O and hexanes giving 46 g (32%) of intermediate Compound 1 as a solid.



Compound 2

Compound 2. In a flame dried flask under N_2 blanket, Compound 1 (12.35 g, 41.2 mmol) was dissolved in dry THF (165 mL) and cooled to -78°C . Methyllithium (1.4 M in Et_2O , 30 mL, 42 mmol) was added and the reaction mixture was stirred for 5 min. n-BuLi (1.6 M in hexanes, 26 mL, 42 mmol) was added followed after 10 min by p-methoxybenzenesulfonyl fluoride (8.64 g, 45.4 mmol) which was prepared by
25 standard methods. The cold bath was removed after 10 min and the reaction mixture was allowed to warm to rt over 45 min then quenched with pH 7 sodium phosphate buffer (1 M, 100 mL, 100 mmol). The reaction mixture was extracted with EtOAc and the resulting organic layer was washed with brine and dried with MgSO_4 . After evaporation of the solvent, the crude product was purified by sgc (20%-50%
30 EtOAc/hexanes gradient) to give 10.39 g (65%) of Compound 2 as a solid.

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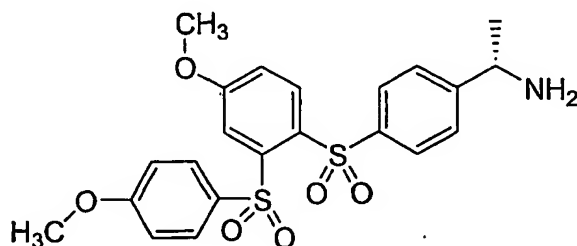


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Compound 3

Compound 3. In a flame dried flask under N₂ blanket, Compound 2 (11.09 g, 28.6 mmol) was dissolved in anhyd THF (100 mL) and cooled to -78°C. A solution of n-BuLi (2.5 M in hexanes, 24 mL, 60 mmol) was added and the reaction mixture was stirred for 40 min. Bis-4-methoxyphenyl disulfide (8.76 g / 31.5 mmol) was added and the reaction mixture was stirred at -78 °C for 40 min then between -15 °C and -30 °C for 5 h then quenched with pH 7.0 sodium phosphate buffer (1.0 M, 120 mL). The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with additional EtOAc. The combined organic layer was washed with aq Na₂CO₃ and brine, then dried with MgSO₄ and concentrated to dryness. The crude product (13.8 g yellow foam) was dissolved in CH₂Cl₂ (120 mL) and cooled to 0°C. MCPBA (18.5 g, ca 107 mmol) was added, followed by additional CH₂Cl₂ (40 mL). The ice bath was removed and the reaction mixture was stirred at rt for overnight. Aqueous NaHCO₃ (200 mL) and CH₂Cl₂ were added and the layers were separated. The organic layer was washed with aq NaHSO₃, NaHCO₃, H₂O, and brine then dried with MgSO₄. The crude product was purified by sgc (30% to 50% EtOAc/hexanes gradient) to give 7.21 g (45%) of Compound 3.

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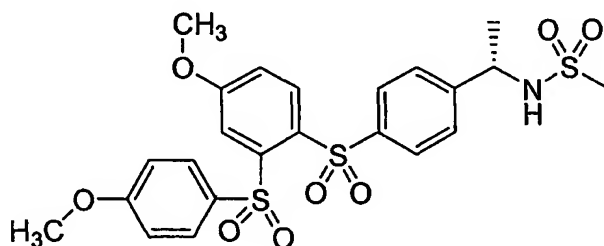


Compound 4

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Compound 4. Compound 3 (4.47 g, 8.02 mmol) was dissolved in p-dioxane (16 mL) and cooled to 0 °C. LiOH (1.0 M aq, 10 mL, 10 mmol) was added and the ice bath was removed. The reaction mixture was stirred at rt for 6 h then concentrated. CH₂Cl₂ (100 mL) and NaOH (1.0 M aq, 10 mL) were added and the layers were
5 separated. The aqueous layer was extracted with additional CH₂Cl₂ and the combined organic layer was dried with MgSO₄ and concentrated. The crude product was purified by sgc (2%-10% MeOH (NH₃)/CH₂Cl₂ gradient mobile phase) to give 3.23 g (87%) of Compound 4.

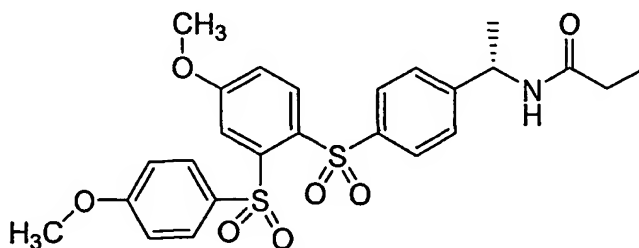
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Compound I

Compound I. Compound 4 (3.08 g, 6.67 mmol) was dissolved in CH₂Cl₂ (33 mL) and triethylamine (1.40 mL, 10.0 mmol) then cooled to 0 °C. MsCl (569 μL, 7.34 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h and 15 min. Citric acid (0.5 M, 40 mL) and additional CH₂Cl₂ were added and the layers were separated. The organic layer was washed with citric acid, NaHCO₃, and
20 brine then dried with MgSO₄. The solvent was evaporated and the crude product was purified by sgc (40%-70% EtOAc/hexanes gradient) to give 3.44 g (96%) of Compound I as a solid.

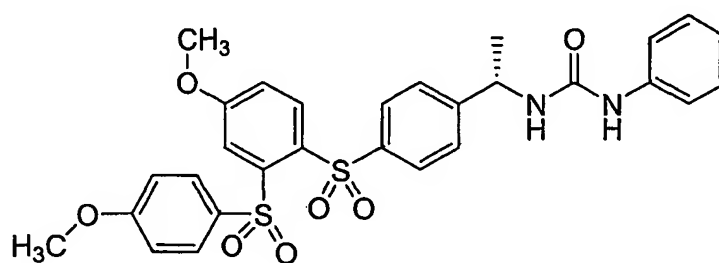
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Compound II

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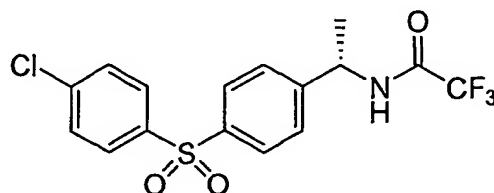
Compound II. Compound 4 (27.5 mg, 0.0595 mmol) was dissolved in methylene chloride (226 μ L) and DIPEA (12 μ L). A solution of propionyl chloride dissolved in 1,2-dichloroethane (1 M, 75 μ L, 0.075 mmol) was added and the reaction mixture was shaken at room temperature overnight. Tris(2-aminoethyl)amine
5 polystyrene (4.1 mmol N/g, ca 60 mg) was added to the reaction mixture. The reaction mixture was shaken for an additional hour at rt. The crude product was concentrated, then dissolved in EtOAc and filtered through a silica-gel SepPak (Waters Corp.). The resulting filtrate was concentrated to give 9 mg (29%) of Compound II.



Compound III

Compound III. Compound 4 (25 mg, 0.054 mmol) was dissolved in CH_2Cl_2 (270 μ L). A solution of phenyl isocyanate dissolved in toluene (1.0 M, 65 mL, 0.065 mmol) was added and the reaction mixture was shaken at rt overnight. Tris
(2-aminoethyl) amine polystyrene (4.1 mmol N/g, ca 60 mg) was added to the reaction mixture and the reaction mixture was shaken for an additional 40 min at rt. EtOAc
20 was added and the reaction mixture was filtered through a silica gel SepPak (Waters Corp.). The resulting filtrate was concentrated to give 18 mg (57%) of Compound III.

EXAMPLE II

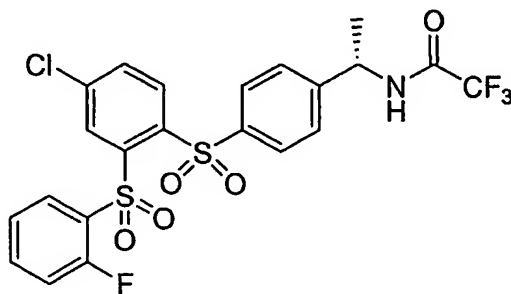


Compound 5

Compound 5. In a 3-necked flame-dried flask under N_2 blanket Compound 1 (40.0 g, 134 mmol) was dissolved in anhyd THF (535 mL) and cooled to -75°C

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(internal temperature). A solution of methyllithium (1.4 M in diethyl ether, 105 mL, 147 mmol) was added at a rate that kept the internal temperature below -60 °C. The reaction was stirred for 15 min and a solution of n-BuLi (2.5 M in hexanes, 62 mL, 155 mmol) was added at a rate that maintained the internal temperature of the reaction below -65 °C. The reaction mixture was stirred for 40 min. and a solution of bis(4-chlorophenyl) disulfide (42 g, 146 mmol) dissolved in anhyd THF (90 mL) was added via addition funnel over 1 h. The reaction mixture was stirred for 3 h then quenched with HCl (1 M aqueous, 200 mL, 200 mmol). EtOAc (500 mL) was added and the layers were separated. The aqueous layer was extracted with 500 mL EtOAc, and the combined organic layer was washed with 1 M aq KOH, water, and brine. After drying with MgSO₄, the solvent was evaporated to give 54.1 g of a solid. The crude product (52.3 g) was dissolved in CH₂Cl₂ (750 mL) and cooled to 2 °C (internal temp). MCPBA (60%, 184 g) was added in portions over 1 hr and 20 min keeping the internal temperature below 15 °C. The reaction mixture was stirred an additional 2 h. NaOH (1 M aq, 500 mL) and CH₂Cl₂ were added and the layers were separated. The aqueous layer was extracted with an additional 300 mL of CH₂Cl₂. The combined organic layer was washed with 1M aqueous NaOH, water, and brine, then dried with MgSO₄. After evaporation of the solvent, a solid (65 g) was obtained. The crude product was partially purified by trituration from Et₂O/hexanes to give 33.3 g of a solid which was subsequently purified via sgc (20%-25% EtOAc/hexanes) to give 30 g (57%) of Compound 5 as a solid.



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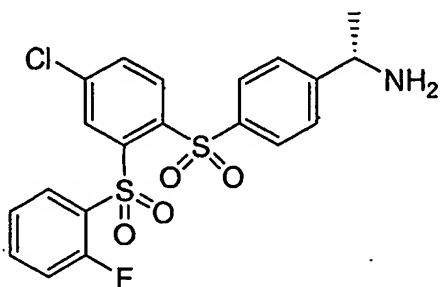
Compound 6

Compound 6. In a flame dried 3-necked flask under N₂ blanket Compound 5 (44 g, 112 mmol) was dissolved in anhyd THF (450 mL) and cooled in a dry ice/IPA bath. A solution of n-butyl lithium (2.5 M in hexanes, 92 mL, 230 mmol) was added at a rate that maintained the internal reaction temperature below -60 °C, and the reaction mixture was stirred for 1 h. A solution of 2-fluorobenzenesulfonyl fluoride (22.3 g, 125 mmol) dissolved in anhyd THF (20 mL) was added and the reaction

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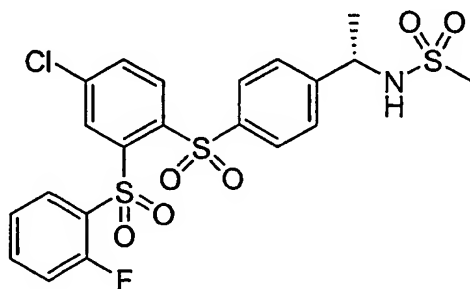
mixture was left stirring overnight and allowed to warm to rt. The reaction mixture was cooled to 0 °C and quenched with saturated aq ammonium chloride (300 mL). EtOAc (600 mL) and brine (25 mL) were added and the layers were separated. The organic layer was washed with water and brine, then dried with MgSO₄. The solvents were
5 evaporated giving a foam (62 g). The product was purified by sgc (20%-25% EtOAc/hexanes mobile phase) giving 9.1 g (15%) of Compound 6.



10

Compound 7

Compound 7. Compound 6 (6.77 g, 12.3 mmol) was dissolved in dioxane (15 mL) and cooled in an ice bath. Aqueous lithium hydroxide (1 M, 15 mL, 15 mmol) was added and the reaction mixture was left stirring overnight. The reaction mixture was
15 concentrated, then partitioned between CH₂Cl₂ and water. The aqueous layer was extracted with additional CH₂Cl₂ and the combined organic layer was dried with MgSO₄. Evaporation of the solvent afforded 5.66 g of a foam which was purified by sgc (10% MeOH (NH₃)/CH₂Cl₂) to give 4.27 g of Compound 7 (77%).



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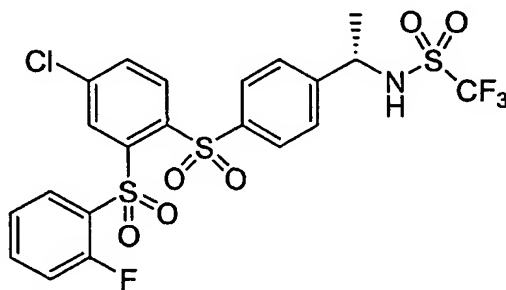
Compound IV

Compound IV. Compound 7 (2.66 g, 5.86 mmol) was dissolved in CH₂Cl₂ (28 mL) and triethylamine (0.98 mL) and cooled to 0 °C. MsCl (0.499 mL, 6.45 mmol) was added and the reaction mixture was stirred at 0 °C for 6 h. The reaction mixture was
25 partitioned between water and CH₂Cl₂. The aqueous layer was extracted with

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additional CH₂Cl₂ and the combined organic layer was dried with MgSO₄. Evaporation of the solvent afforded 3.0 g of a foam which was purified by sgc (40%-50% EtOAc/hexanes gradient) to give 2.77 g (89%) of Compound IV.

- 5 Compound IV : ¹H NMR (300 MHz, CDCl₃) 8.61-5.97 (m, 2H), 8.40 (d, 8 Hz, 1H), 8.24-8.21 (m, 1H), 7.96 (d, 8 Hz, 2H), 7.86-7.83 (m, 1H), 7.70-7.63 (m, 1H), 7.52 (d, 8 Hz, 2H), 7.46-7.40 (m, 1H), 7.18-7.12 (m, 1H), 4.80-4.70 (m, 1H), 2.71 (s, 3H), 1.56 (d, 7Hz, 3H).



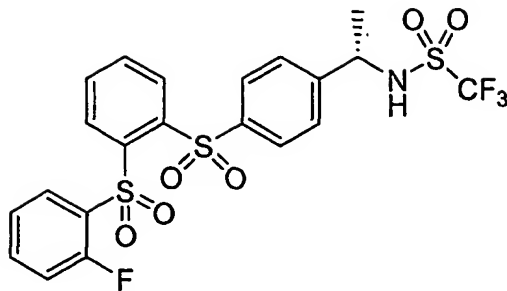
Compound V

- Compound V.** Compound 7 (26.1 g, 57.4 mmol) was dissolved in CH₂Cl₂ (200mL) and triethylamine (20 mL) and cooled to -78°C. Triflic anhydride (10.45 mL, 62.1 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was quenched with water and the layers were separated. The organic layer was washed with water and brine, then dried with MgSO₄. The solvent was evaporated to give 42 g of a foam. The crude product was purified via sgc (33%-50% EtOAc/hexanes gradient) to give 29.7 g (88%) of Compound V.
- 15
- 20

Compound V : ¹H NMR (300 MHz, CDCl₃) 8.61-8.59 (m, 1H), 8.39 (d, 8 Hz, 1H), 8.29-8.24 (m, 1H), 7.99 (d, 8 Hz, 2H), 7.86-7.82 (m, 1H), 7.67-7.62 (m, 1H), 7.49 (d, 8Hz, 1H), 7.46-7.40 (m, 1H), 7.16-7.10 (m, 1H), 4.89-4.84 (m, 1H), 1.65 (d, 6 Hz, 1H).

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- 49 -

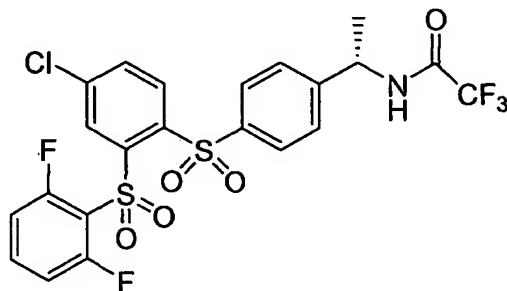


Compound VI

- 5 **Compound VI.** Compound V (300 mg, 0.512 mmol) was dissolved in methanol (60 mL). Sodium bicarbonate (720 mg, 8.57 mmol) and 5% palladium on carbon (480 mg) were added. The reaction mixture was shaken on a Parr apparatus under 52 psi of hydrogen gas overnight. The reaction mixture was filtered and the solvent was evaporated. The resulting material was partitioned between EtOAc and aq NaHCO₃.
- 10 The organic layer was dried with MgSO₄ and the solvents were evaporated. The crude product was purified *via* sgc (33% EtOAc/hexanes) to give 257 mg (91%) of Compound VI.

EXAMPLE III

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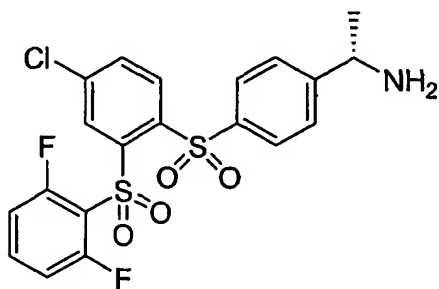


Compound 8

- 20 **Compound 8.** In a flame dried 3-necked flask under N₂ blanket Compound 5 (35.7 g, 91 mmol) was dissolved in anhyd THF (360 mL) and cooled in a dry ice/IPA bath. A solution of n-BuLi (2.5 M in hexanes, 76 mL, 190 mmol) was added at a rate that maintained the internal temperature below -60 °C. The reaction mixture was stirred for 1 h. A solution of 2,6-difluorobenzenesulfonyl fluoride (19.47 g, 99.28 mmol) dissolved in anhyd THF (60 mL) was added. The reaction mixture was stirred for 2.5 h, then quenched with saturated aq NH₄Cl (400 mL). EtOAc (500 mL) was added and the layers were separated. The aq layer was extracted with EtOAc and the
- 25

- 50 -

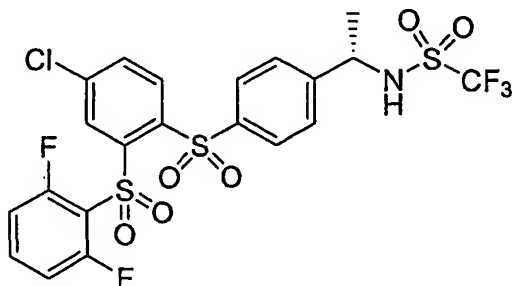
combined organic layer was washed with brine and dried with MgSO_4 . The solvent was evaporated to give 60.7 g of an oil which was purified by sgc (15%-40% EtOAc/hexanes gradient) giving 14.4 g (28%) of Compound 8.



5

Compound 9

Compound 9. Compound 8 (21.1 g, 37.2 mmol) was dissolved in dioxane (47 mL) and aq lithium hydroxide (1.0 M, 41 mL, 41 mmol) was added. After 5.5 h, additional LiOH (20 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was extracted with CH_2Cl_2 , and partitioned between CH_2Cl_2 and water. The aq layer was extracted with additional CH_2Cl_2 and the combined organic layer was dried with MgSO_4 . The solvents were evaporated to give 17.6 g of a foam and the crude product was purified by sgc (1%-3% MeOH (NH_3)/ CH_2Cl_2 gradient) to give 12.2 g (69%) of Compound 9.



20

Compound VII

Compound VII. Compound 9 (10.7 g, 22.6 mmol) was dissolved in a mixture of CH_2Cl_2 (90 mL) and triethylamine (8 mL) and cooled to -78°C . Triflic anhydride (3.80 mL, 22.6 mmol) was added and the reaction mixture was stirred for 2 h. The reaction was quenched with saturated aq NaHCO_3 and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was

- 51 -

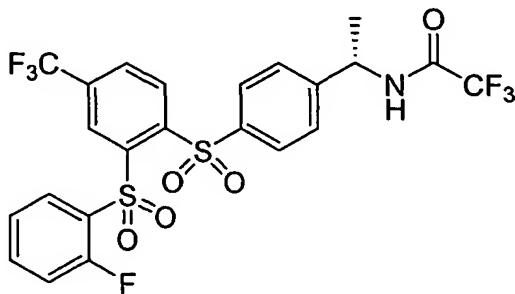
washed with brine and dried with MgSO_4 . The solvents were evaporated and the crude product was purified by sgc to give 9.88 g (73%) of Compound VII.

EXAMPLE IV

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Compound 5. In a flame dried flask under N_2 blanket Compound 1 (39.2 g, 132 mmol) was dissolved in anhyd THF (1 L) and cooled in a dry ice/acetone bath. A solution of methyllithium (1.6 M in Et_2O , 82.7 mL, 132 mmol) was added followed by a solution of n-BuLi (2.5 M in hexanes, 53 mL, 133 mmol). The reaction mixture was stirred for 25 min and a solution of bis(4-trifluoromethylphenyl) disulfide (46.9 g, 132 mmol) dissolved in THF (200 mL) was added. The reaction mixture was stirred for 2 h then allowed to warm to rt overnight. The reaction was quenched with water and concentrated. The resulting mixture was diluted with EtOAc, washed with water, and dried with Na_2SO_4 . The solvent was evaporated and the crude product was purified via sgc (20% EtOAc/hexanes) to give 49.2 g (95%) of a solid. This material (49.2 g) was dissolved in CH_2Cl_2 (1.2 L) and cooled in an ice bath. MCPBA (60%, 90 g) was added in small portions. After 1 h, the ice bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous NaHCO_3 . The combined organic layer was washed with water and dried with Na_2SO_4 . The solvent was evaporated and the crude product was purified by sgc (25% EtOAc/hexanes) to give 46.3 g (85%) of Compound 5.

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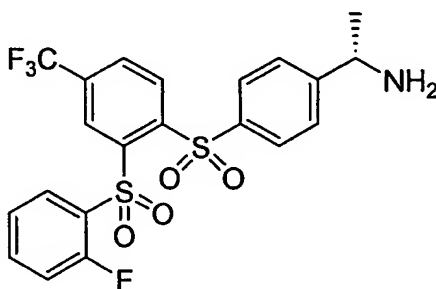
Compound 10

Compound 10. In a flame dried flask under N_2 blanket, Compound 5 (21.55 g, 50.7 mmol) was dissolved in anhyd THF (300 mL) and cooled in a dry ice/IPA bath. A solution of methyllithium (1.6 M in Et_2O , 32 mL, 51 mmol) was added, followed by n-BuLi (2.5 M in hexanes, 20.3 mL, 50.7 mmol) and the reaction mixture was stirred for

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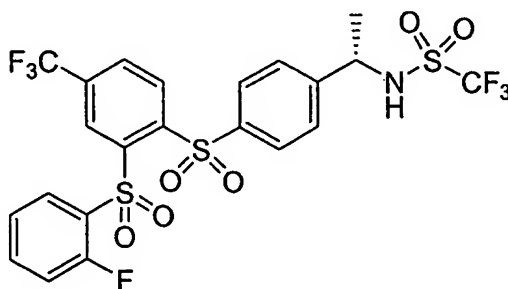
- 52 -

10 min. A solution of bis-(2-fluorophenyl) disulfide (14.2 g, 55.7 mmol) dissolved in THF was added and the reaction mixture was stirred for 2 h at -78°C . The ice bath was removed and the reaction mixture was allowed to warm to rt and left stirring overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl and
5 extracted with EtOAc. The organic layer was dried with Na_2SO_4 and the solvents were evaporated. The crude product was purified via sgc (25% EtOAc/hexanes) to give 23.2 g of a solid. This material was dissolved in CH_2Cl_2 (400 mL) and cooled in an ice bath. MCPBA (60%, 30.3 g) was added in several portions and the reaction mixture was stirred for 1 h. The ice bath was removed and the reaction mixture was
10 left stirring overnight. The reaction mixture was partitioned between CH_2Cl_2 and 5% aq Na_2CO_3 . The organic layer was washed with water and dried with Na_2SO_4 . The solvents were evaporated and the crude product was purified *via* sgc (25%EtOAc/hexanes) to give 10.84 g (44%) of Compound 10.



Compound 11

Compound 11. Compound 10 (11.88 g, 20.36 mmol) was dissolved in dioxane (200 mL) and aq lithium hydroxide (1.0 M, 400 mL) was added. The reaction mixture
20 was stirred for 3 h then and partitioned between CH_2Cl_2 and water. The organic layer was dried with Na_2SO_4 and concentrated to give 9.34 g (99%) of Compound 11.



Compound VIII

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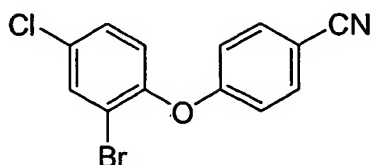
Compound VIII. Compound 11 (0.63 g, 1.29 mmol) was dissolved in a mixture of CH_2Cl_2 (60mL) and triethylamine (0.27 mL) and cooled in an ice bath. Triflic

- 53 -

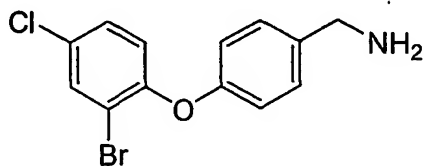
anhydride (0.55 g, 1.95 mmol) was added and the reaction mixture was stirred for 1 h. The ice bath was removed, and the reaction mixture was stirred an additional 3 h. The reaction was partitioned between water and CH₂Cl₂. The organic layer was washed with water and dried with Na₂SO₄. The solvent was evaporated and the crude product was purified by sgc (20% EtOAc/hexanes) to give 0.53 g (66%) of Compound VIII.

Compound VIII : ¹H NMR (300 MHz, CDCl₃) 8.89-8.87 (m, 1H), 8.58 (d, 8Hz, 1H), 8.32-8.25 (m, 1H), 8.15-8.11 (m, 1H), 8.03-7.98 (m, 2H), 7.71-7.63 (m, 1H), 7.52-7.48 (m, 2H), 7.47-7.41 (m, 1H), 7.16-7.09 (m, 1H), 5.62 (d, 8 Hz, 1H), 4.90-4.80 (m, 1H), 1.63 (d, 7 Hz, 3H).

EXAMPLE V



Potassium hydroxide (3.1 g, 55.2 mmol), 2-bromo-4-chlorophenol (9.52 g, 45.9 mmol), and 4-fluorobenzonitrile (5.73 g, 47.3 mmol) were added to DMA (25 mL) and the reaction mixture was stirred between 100 °C and 110 °C for one week. The reaction mixture was stirred at rt an additional two days. The solvents were partially removed on the rotary evaporator and the resulting mixture was partitioned between water and a 3:1 Et₂O/hexanes solution. The organic layer was washed with water and brine, then dried with MgSO₄. The solvents were evaporated and the crude product was purified by sgc (20%-30% CH₂Cl₂/hexanes) to give 11.96 g (81%) of an oil.



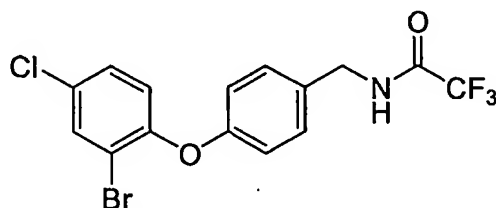
Compound 12

Compound 12. The product of the above step (5.90 g, 19.1 mmol) was placed under N₂ atmosphere and a solution of borane in THF (1.0 M, 21 mL, 21 mmol) was

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added causing an exotherm. Once the reaction mixture had returned to rt, it was heated to reflux and stirred at reflux overnight. Additional borane in THF (1.0 M, 20 mL, 20 mmol) was added and the reaction mixture was stirred at reflux for an additional 26 h then allowed to cool to rt. Water (55 mL) was added and the reaction mixture was partially concentrated. The resulting mixture was partitioned between EtOAc and aq NaOH (1.0 M). The organic layer was dried with MgSO₄ and concentrated to give 6.2 g of an oil. This material was dissolved in Et₂O and a solution of HCl in Et₂O was added causing Compound 12 (5.2 g, 78%) to precipitate as a solid.

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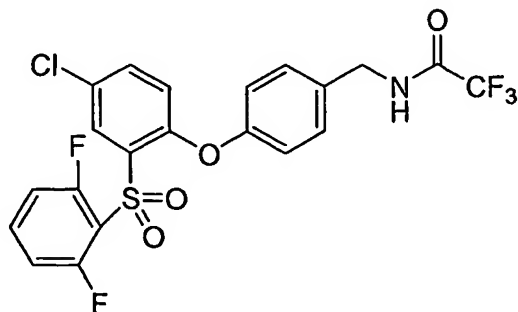


Compound 13

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Compound 13. Compound 12 (5.13 g, 16.6 mmol) was suspended in a mixture of CH₂Cl₂ (40 mL) and triethylamine (7.5 mL). The mixture was cooled in an ice-water bath and TFAA (2.35 mL, 16.6 mmol) was added. The reaction mixture was stirred for 1 h and 20 min and the ice bath was removed. The reaction mixture was stirred for an additional 1 h and 20 min at rt. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed with aq citric acid (0.5 M), saturated aq NaHCO₃, water, and brine, then dried with MgSO₄. The solvents were evaporated and the crude product (5.22 g) was purified *via* sgc (10%-20% EtOAc/hexanes gradient) to give Compound 13.

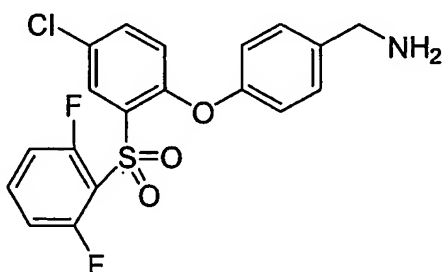
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Compound 14

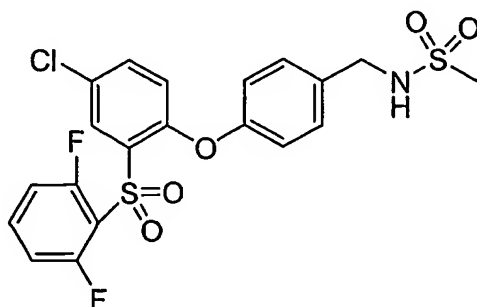
- 55 -

Compound 14. In a flame dried flask under N₂ blanket, Compound 13 (1.00 g, 2.47 mmol) was dissolved in anhyd THF (13 mL) and cooled in a dry ice/IPA bath. Methyllithium (1.4 M in Et₂O, 2.3 mL, 3.22 mmol) was added, followed by n-BuLi (2.5 M in hexanes, 1.3 mL, 3.25 mmol). The reaction mixture was stirred for 1 h at -78 °C. A solution of 2,6-difluorobenzenesulfonyl fluoride (1.10 g, 5.60 mmol) dissolved in THF was added and the reaction mixture was stirred for 4 h. The reaction mixture was quenched with pH 7 sodium phosphate buffer (1.0 M) and EtOAc was added. The layers were separated and the aqueous layer was extracted with additional EtOAc. The combined organic layer was washed with brine and dried with MgSO₄. The solvents were evaporated and the crude product was purified via sgc (20%-33% EtOAc/hexanes) gradient to give 76 mg of Compound 14.



Compound 15

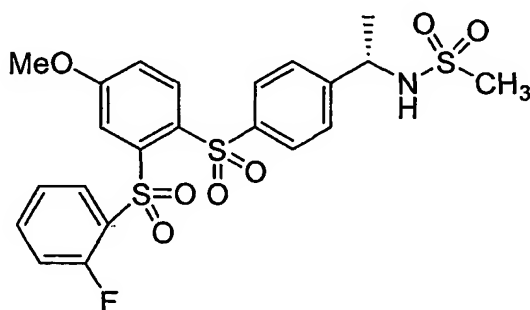
Compound 15. Compound 14 (59 mg, 0.12 mmol) was dissolved in 700 µL of dioxane and LiOH (1.0 M, 300 µL, 0.3 mmol) was added. The reaction mixture was stirred at rt for 24 h then partitioned between CH₂Cl₂ and 1.0 M aq NaOH. The organic layer was dried with MgSO₄ and concentrated. The crude product was purified via PTLC (Merck- silica plates, 3% (MeOH/NH₃)/CH₂Cl₂) to give the desired Compound 15. (21 mg, 45%).



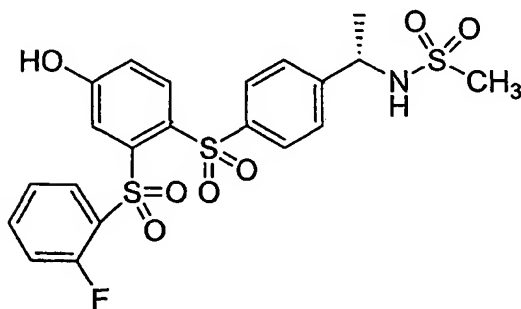
Compound IX

Compound IX. Compound 15 (17 mg, 0.042 mmol) was dissolved in CH_2Cl_2 (166 μL) and DIPEA (20 μL). The flask was cooled in an ice/water bath and MsCl (12 μL , 0.15 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and 30 min. The resulting mixture was partitioned between water and CH_2Cl_2 . The organic layer was washed with water and brine, then dried with MgSO_4 . The crude product was purified *via* PTLC (50 % EtOAc/hexanes) to give 10 mg (50%) Compound IX.

EXAMPLE VI



Compound 16

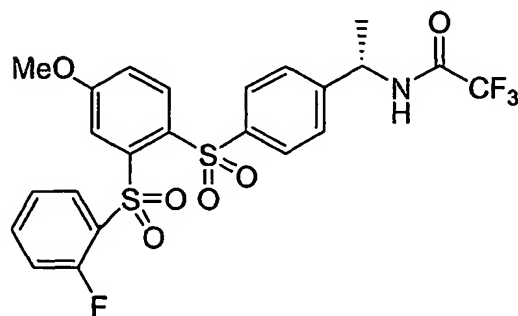


Compound X

Compound 16 (0.116 g, 0.22 mmoles) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. BBr_3 solution (1.0 M in CH_2Cl_2 , 0.66 mL) was added and the ice bath was removed. The reaction mixture was stirred at rt for 48 h and then quenched with water at -78 °C. The reaction mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed with aqueous NaHCO_3 , H_2O (3 X 5 mL), and brine. The organics were dried over Na_2SO_4 and the solvent was removed under vacuum to give 0.09 g of crude product. The product was isolated by PTLC (5% CH_3OH / CH_2Cl_2) to provide Compound X (0.01g, 8.8%).

Compound 16 : ^1H NMR (300 MHz, CDCl_3) 1.54 (d, $J = 6.9\text{Hz}$ 3H), 2.67 (s, 3H), 4.72 (q, $J = 5\text{Hz}$ 1H), 4.86 (br. d, $J = 5\text{Hz}$, 1H, NH), 7.08-8.42 (m, 11H).

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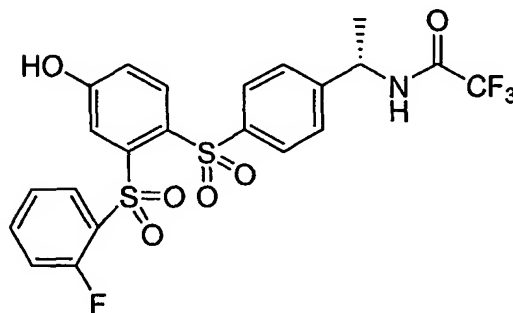
EXAMPLE VII

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Compound 17

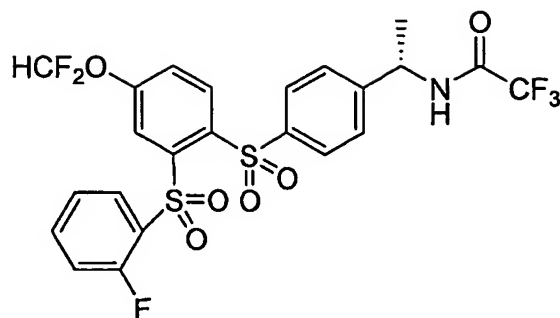
Compound 17 was converted to Compound 18 using the procedure in example VI.

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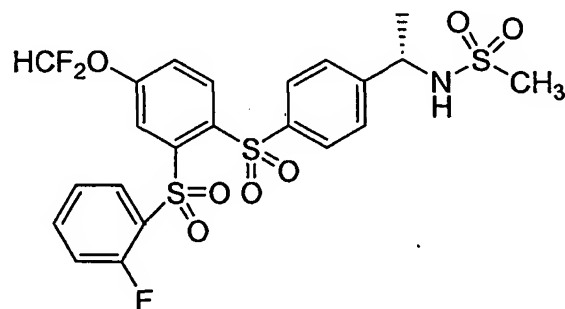
Compound 18

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Compound 19

5 **Compound 18** (0.34 g, 0.64 mmoles) was dissolved in DMF (11 mL), cesium carbonate (0.84 g, 2.58 mmol) was added and the reaction mixture was cooled to 15 °C. Dry bromodifluoromethane gas was introduced into the solution and bubbled for 15-20 min. Progress of the reaction was monitored by TLC and upon completion the reaction mixture was diluted with EtOAc (20 mL), washed with water (4 X 10 mL), and
 10 brine. The organics were dried over Na₂SO₄ and concentrated under reduced pressure to give 0.36 g of an oil. The crude product was purified by PTLC (50% EtOAc/hexanes) to provide 0.31 g (83%) of Compound 19.



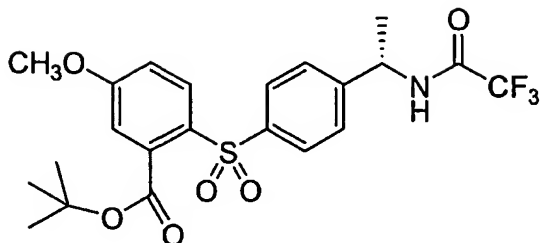
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Compound XI

20 **Compound 19** was converted to Compound XI using the procedure in example II.

Compound XI : ¹H NMR (400 MHz, CDCl₃) 1.51 (d, J = 7.2Hz 3H), 2.67 (s, 3H), 4.702 (q, J = 6.8Hz 1H), 5.05 (br. d, J = 6.4Hz, 1H, NH), 6.71 (t, J = 71.6 Hz, CF₂H) 7.07-8.47 (m, 11H).

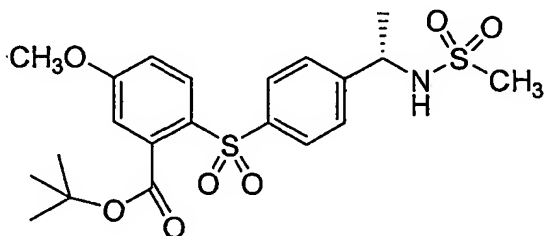
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EXAMPLE VIII

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Compound 20

Compound 20. To a solution of Compound 2 (5.00 g, 12.9 mmol) in anhyd THF (75 mL) at -78 °C was added *n*-BuLi (13 mL, 2.5 M in hexanes, 32 mmol) dropwise over 10 min. The reaction mixture was stirred for 30 min. A solution of di-*t*-butyl dicarbonate (3.10 g, 14.2 mmol) in anhyd THF (25 mL) was added in one portion via cannula. The reaction was allowed to proceed for 4 h at -78 °C. The reaction mixture was then diluted with EtOAc (~250 mL) and washed successively with saturated aq NaHSO₄ (~100 mL), water (~100 mL), and brine (~100 mL). The organic layer was dried over anhyd MgSO₄, filtered, and concentrated under reduced pressure to yield a solid. Further purification of the solid by sgc (25% EtOAc/hexanes) gave 5.32 g (84%) of Compound 20 as a solid.



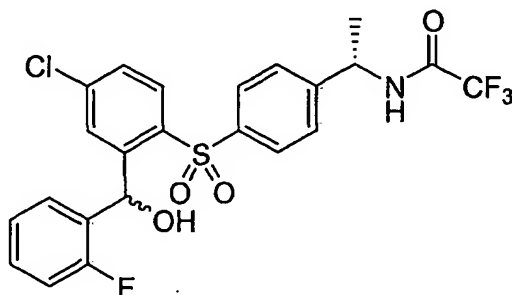
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Compound XII

Compound XII. Compound 20 (2.06 g, 4.23 mmol) was dissolved in methanol (40 mL) and a solution of potassium carbonate (2.92 g, 21.1 mmol) in water (10 mL) was added. The reaction was allowed to proceed for 18 h. The solvent was then removed by evaporation under reduced pressure. The resulting white solid was partitioned between water (~100 mL) and EtOAc (~400 mL). The aqueous layer was extracted further with EtOAc (~100 mL). The combined organic layers were washed with brine (~500 mL), then dried over anhyd MgSO₄ and filtered. Evaporation of the

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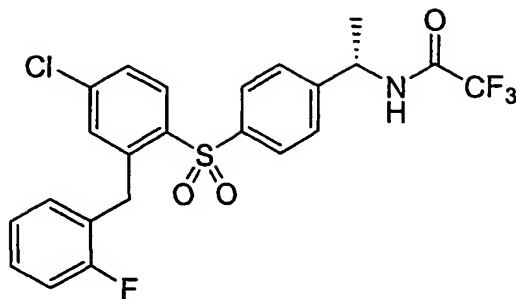
solvent gave 1.22 g (74%) of *t*-butyl 2-[(4-(1(*S*)-aminoethyl)phenyl)sulfonyl-5-methoxybenzoate, an oil, which was used in the next step without further purification. MsCl (242 μ L, 357 mg, 3.12 mmol) was added dropwise to a solution of crude *t*-butyl 2-[(4-(1(*S*)-aminoethyl)phenyl)sulfonyl-5-methoxybenzoate (1.22 g, 3.12 mmol) and triethylamine (522 μ L, 379 mg, 3.75 mmol) in anhyd CH_2Cl_2 (3.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, then allowed to warm to rt, and subsequently stirred for 3 h. The reaction mixture was diluted with CH_2Cl_2 (~50 mL) and washed successively with 1 M HCl (~50 mL), water (3 x ~50 mL) and brine (~50 mL). The organic solution was dried over anhyd MgSO_4 , filtered, and concentrated to yield a solid. Subsequent purification of the crude product by sgc (25% EtOAc/hexanes) gave 1.41 g (96%) of Compound XII as a solid.

EXAMPLE IX

Compound 21

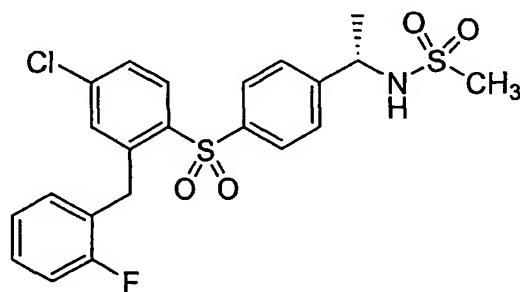
Compound 21. In a flame dried flask under N_2 blanket, Compound 5 (400 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and cooled to -78°C . A solution of *n*-BuLi (1.0 M in hexanes, 1.9 mL, 1.9 mmol) was added and the reaction mixture was stirred for 30 min. 2-Fluorobenzaldehyde (200 mg, 1.6 mmol) was added and the reaction mixture was stirred at -78°C for 3 h. The reaction mixture was then quenched with saturated aq NH_4Cl (20 mL). Methylene chloride (30 mL) was added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4 , and concentrated to dryness. The crude product was purified via sgc (25% EtOAc/hexanes) to give 330 mg (62%) of Compound 21 as a powder.

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Compound 22

- 5 **Compound 22.** Compound 21 (10 mg) was dissolved in CH_2Cl_2 (10 mL). Triethylsilane (40 μL , 0.25 mmol) was added followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (20 μL , 0.16 mmol). The reaction mixture was stirred at rt overnight. After removing the solvent, the crude product was purified via PTLC (25% EtOAc/hexanes) to give 6.0 mg (62%) Compound 22 as an oil.

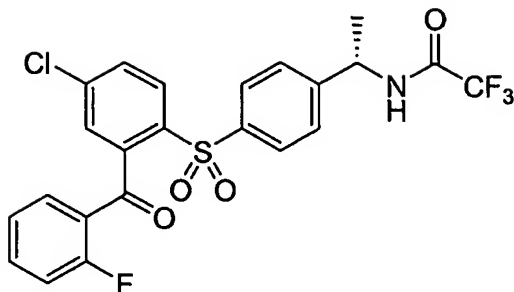


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Compound XIII

- 15 **Compound XIII.** Compound 22 (12 mg) was dissolved in methanol (2 mL) at rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 2 h. The solvent was removed, CH_2Cl_2 (15 mL) and brine (15 mL) were added, and the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2 (15 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude product was then dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C.
- 20 MsCl (14 μL , 0.18 mmol) was added followed by addition of pyridine (30 μL , 0.37 mmol). The reaction mixture was slowly warmed to rt and stirred overnight. Brine (15 mL) was added and extracted. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (25% EtOAc/hexanes) to give 10 mg (86%) of Compound XIII as an oil.

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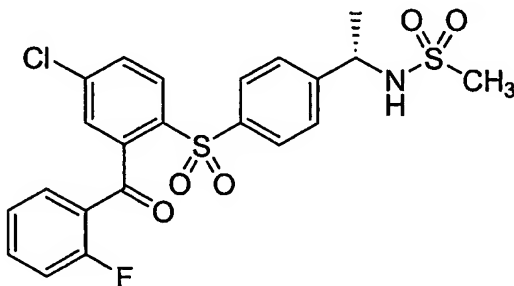
EXAMPLE X

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Compound 23

Compound 23. Compound 21 (330 mg, 0.64 mmol) was dissolved in CH₂Cl₂ (20 mL) at rt. Celite (450 mg) was added followed by addition of PCC (450 mg, 2.1 mmol). The mixture was stirred at rt overnight. The solid was removed by filtration and the organic layer was washed with aq. NaHCO₃ and brine. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The crude product was purified via sgc (33% EtOAc/hexanes) to give 310 mg (94%) of Compound 23 as a powder.

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Compound XIV

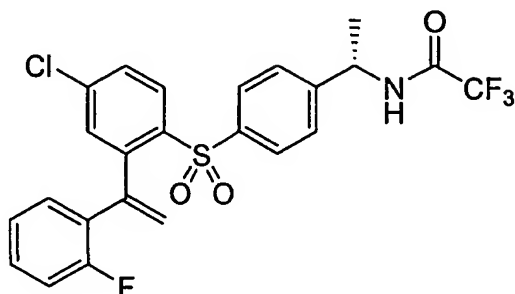
Compound XIV. Compound 23 (15 mg) was dissolved in methanol (2 mL) at rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 2 h. The solvent was removed and CH₂Cl₂ (15 mL) and brine (15 mL) were added and the layers separated. The aq layer was extracted with additional CH₂Cl₂ (15 mL) and the combined organic layer was dried over Na₂SO₄ and concentrated to dryness. The crude product was then dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C. MsCl (15 μL, 0.19 mmol) was added followed by addition of pyridine (30 μL, 0.37 mmol). The reaction mixture was slowly warmed to rt and stirred overnight. Brine (15 mL) was added and extracted. The organic layer was dried over Na₂SO₄ and concentrated to

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- 63 -

dryness. The crude product was purified via PTLC (33% EtOAc/hexanes) to give 9 mg (62%) of Compound XIV as an oil.

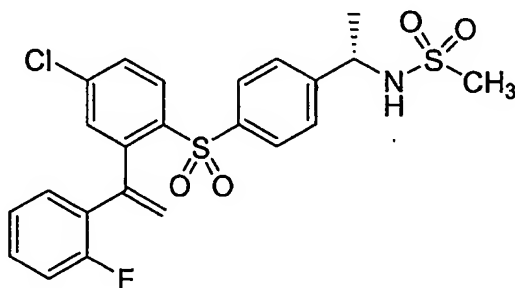


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Compound 24

Compound 24. Oven dried methyltriphenylphosphonium bromide (430 mg, 1.2 mmol) and LHDMS (1.0 M in hexanes, 1.8 mL, 1.8 mmol) were stirred in dry THF (5 ml) at 0 °C for 20 min., then warmed to rt and stirred for 10 min. A solution of Compound 23 (300 mg, 0.58 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at rt overnight. EtOAc (20 ml) was added and the organic solution was washed with brine. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The crude product was purified via PTLC (25% EtOAc/hexanes) to give 260 mg (87%) of Compound 24 as an oil.

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Compound XV

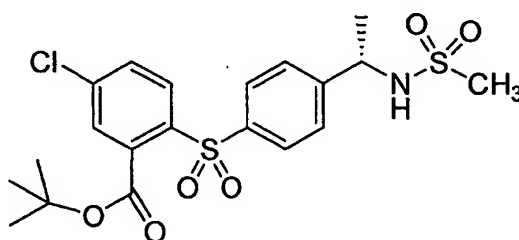
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Compound XV. Compound 24 (200 mg, 0.39 mmol) was dissolved in methanol (3 mL) at rt. NaOH (1.0 M, 3 mL, 3.0 mmol) was added and the mixture was stirred at 50 °C for 2 h. The solvent was removed, CH₂Cl₂ (20 mL) and brine (20 mL) were added, and the layers were separated. The aqueous layer was extracted with additional CH₂Cl₂ (15 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude product was then dissolved in CH₂Cl₂

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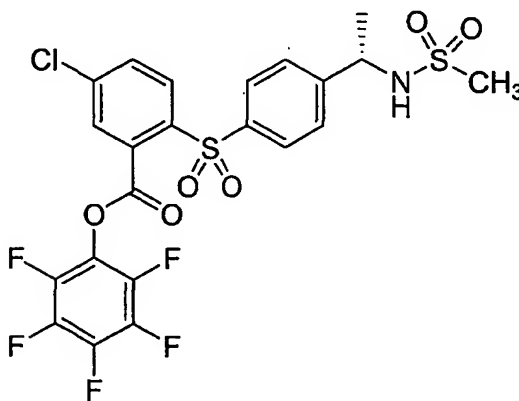
- 64 -

(15 mL) and cooled to 0 °C. MsCl (200 μ L, 2.5 mmol) was added followed by addition of pyridine (400 μ L, 4.9 mmol). The reaction mixture was slowly warmed to rt and stirred overnight. Brine (15 mL) was added and the organic layer separated, dried over Na₂SO₄ and concentrated to dryness. The crude product was purified via PTLC (50% EtOAc/hexanes) to give 160 mg (82%) of Compound XV as an oil.

EXAMPLE XI

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Compound 25



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Compound 26

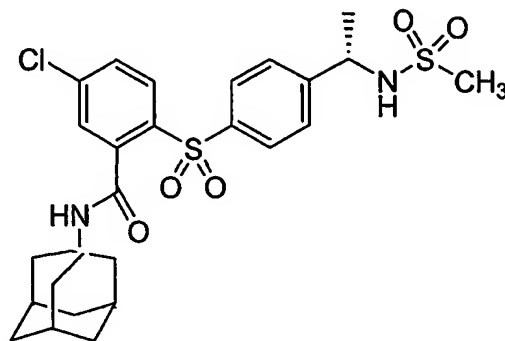
Compound 26. Compound 25 (1.3 g, 2.7 mmol) was stirred at rt with a mixture of CH₂Cl₂/TFA (2:1, 30 mL) for 3 h. The reaction mixture was then poured into brine (40 mL). The layers were separated. The aq layer was extracted with CH₂Cl₂ (3 X 30 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude product was dissolved in CH₂Cl₂ (30 mL). EDCI (0.75 g, 3.9 mmol) and pentafluorophenol (0.73 g, 4.0 mmol) were added and the mixture was stirred at rt overnight. The reaction mixture was extracted with diluted aq NaOH and washed with brine. The organic layer was then dried over Na₂SO₄ and concentrated

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- 65 -

to dryness. The crude product was purified via sgc (33% EtOAc/hexanes) to give 1.15 g (72%) of Compound 26 as a foam.



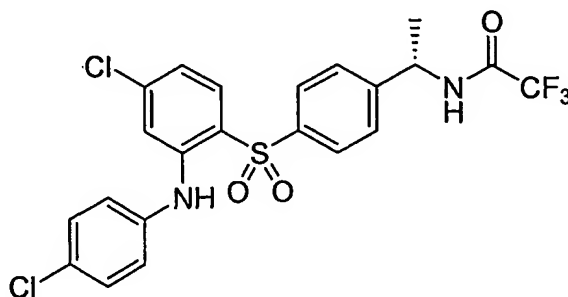
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Compound XVI

Compound XVI. Compound 26 (50 mg) was dissolved in CH_2Cl_2 (2 mL). 1-Adamantanamine (21 mg, 0.14 mmol) was added followed by addition of DIPEA (0.05 mL, 0.29 mmol). The reaction mixture was shaken overnight. The reaction mixture was then subjected to Amberlyst 15 resin (300 mg, loading 4.1 mmol/g), and was again shaken overnight. The resin was removed by filtration. The filtrate was subjected to MP carbonate resin (Argonaut Technologies) (100 mg, loading 2.64 mmol/g) for 4 h. The resin was removed by filtration and the filtrate concentrated to give 33 mg (70%) of Compound XVI as a powder.

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EXAMPLE XII



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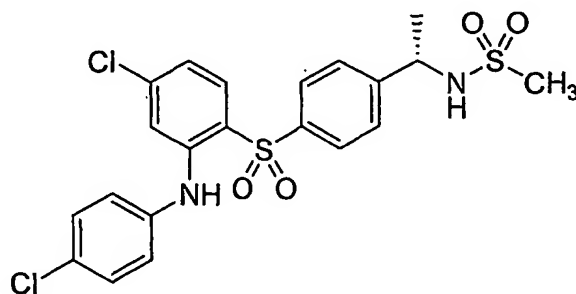
Compound 27

Compound 27. Compound 5 (500 mg, 1.3 mmol) was dissolved in dry THF (6 mL) at rt. NaH (53 mg, 60%, 1.3 mmol) was added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was then cooled to -78°C , and n-BuLi (1.0

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- 66 -

M in hexanes, 1.5 mL, 1.5 mmol) was added dropwise under N₂ atmosphere. The reaction was stirred at -78 °C for 40 min. A solution of I₂ (390 mg, 1.5 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 3 h, then quenched with saturated aq NH₄Cl (20 mL). EtOAc (30 mL) was added and the
5 layers were separated. The organic layer was washed with brine, then dried over Na₂SO₄, and concentrated to dryness. The crude product (640 mg) was used without further purification. The crude product (60 mg) was dissolved in toluene (2 mL) and Pd(OAc)₂ (2 mg), P^tBu₃ (1 drop), NaO^tBu (14 mg, 0.15 mmol) and *p*-Chloroaniline (13 mg, 0.11 mmol) were added. The mixture was kept in a sealed tube and heated
10 to 120 °C for 20 h. After cooling, methylene chloride (30 mL) and brine (20 mL) were added and the layers were separated. The organic layer was washed with brine, then dried over Na₂SO₄, and concentrated to dryness. The crude product was purified with via PTLC (20% EtOAc/hexanes) to give 18 mg (30 %) of Compound 27 as a powder.

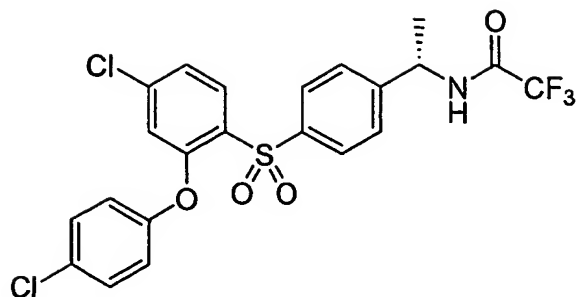


Compound XVII

Compound XVII. Compound 27 (12 mg) was dissolved in methanol (2 mL) at
20 rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 3 h. The solvent was removed, CH₂Cl₂ (20 mL) and brine (20 mL) were added, and the layers were separated. The aq layer was extracted with additional CH₂Cl₂ (15 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude product was then dissolved in CH₂Cl₂ (15mL) and cooled to 0 °C.
25 MsCl (15 µL, 0.19 mmol) and pyridine (30 µL, 0.37 mmol) were added. The reaction mixture was slowly warmed up to rt and stirred overnight. Brine (15 mL) was added and the reaction mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The crude product was purified via PTLC (33% EtOAc/hexanes) to give 6.0 mg (52%) of Compound XVII as an oil.

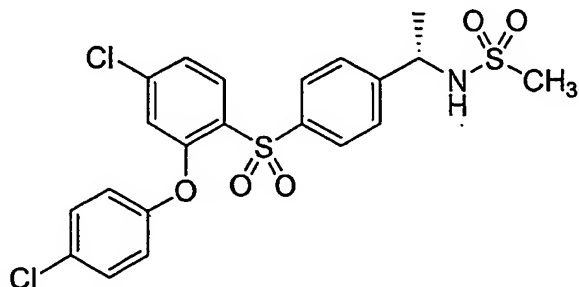
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Compound 28

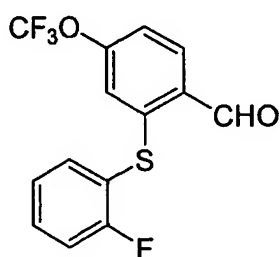
- 5 **Compound 28.** Compound 5 (500 mg, 1.3 mmol) was dissolved in dry THF (6 mL) at rt. NaH (53 mg, 60%, 1.3 mmol) was added, and the mixture was stirred at rt for 1 h. The reaction mixture was cooled to -78°C , and *n*-BuLi (1.0 M, 1.5 mL, 1.5 mmol) was added dropwise under N_2 atmosphere, and the temperature was maintained at -78°C for 40 min. A solution of I_2 (390 mg, 1.5 mmol) in THF (2 mL)
- 10 was added dropwise. The reaction was stirred at -78°C for 3 h. The reaction mixture was quenched with saturated aq NH_4Cl (20 mL). EtOAc (30 mL) was added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4 , and concentrated to dryness. The crude product (640 mg) was used without further purification. The crude product (60 mg) was dissolved in toluene (2 mL) and
- 15 NaH (5 mg, 60%, 0.12 mmol), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (34 mg, 0.17 mmol) and *p*-chlorophenol (15 mg, 0.12 mmol) were added. The reaction mixture was kept in a sealed tube and heated to 120°C overnight. After cooling, CH_2Cl_2 (30 mL) and brine (20 mL) were added and the layers were separated. The organic layer was washed with brine, then dried over Na_2SO_4 , and concentrated to dryness. The crude product was purified via
- 20 PTLC (20% EtOAc/hexanes) to give 19 mg (31 %) of Compound 28 as a powder.



Compound XVIII

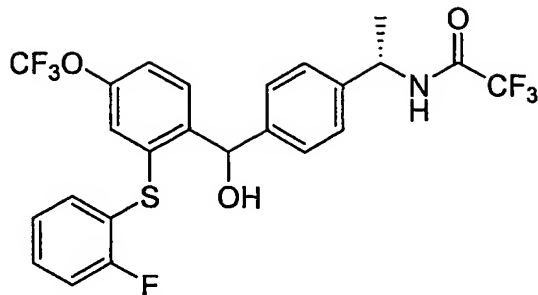
- 68 -

Compound XVIII. Compound 28 (15 mg, 29 μ mol) was dissolved in methanol (2 mL) at rt. NaOH (1.0 M, 2 mL, 2.0 mmol) was added and the mixture was stirred at rt for 2 h. The solvent was removed and CH_2Cl_2 (20 mL) and brine (20 mL) was added and the layers were separated. The aq layer was extracted with additional CH_2Cl_2 (15 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was then dissolved in CH_2Cl_2 (15 mL) and cooled to 0 $^\circ\text{C}$. MsCl (20 μ L, 0.25 mmol) was added followed by addition of pyridine (20 μ L, 0.25 mmol). The reaction mixture was slowly warmed up to rt and stirred overnight. Brine (15 mL) was added and extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude product was purified via PTLC (50% EtOAc/hexanes) to give 7.0 mg (48%) of Compound XVII as an oil.

EXAMPLE XIIICompound 29

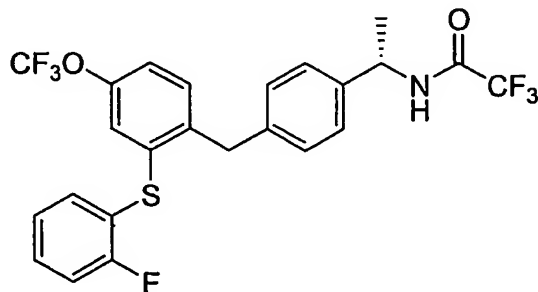
Compound 29. To a solution of N,N,N-Trimethylethylenediamine (1.2 mL, 8.6 mmol) in THF (8 mL) at -20 $^\circ\text{C}$ was added n-BuLi (1.6 M, 5.4 mL, 8.6 mmol) dropwise. After 15 min 4-trifluoromethoxybenzaldehyde (1.5 g, 7.8 mmol) in THF (8 mL) was added. The mixture was stirred for 15 minutes and additional n-BuLi (1.6M, 14.6 mL, 23 mmol) was added. The reaction mixture was stirred at -20 $^\circ\text{C}$ for 1h, then placed in the freezer at -20 $^\circ\text{C}$ for 20 h. The mixture was cooled to -40 $^\circ\text{C}$, and a solution of bis(2-fluorophenyl)disulfide (4.0 g, 15.7 mmoles) in 30 mL THF was added. The reaction mixture was stirred at -35 $^\circ\text{C}$ for 3 h. The reaction mixture was poured into 0.5 N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated to an oil. Purification by sgc (3 % EtOAc / hexanes) gave 1.55 g (62 %) of Compound 29 as a solid..

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Compound 30

- 5 **Compound 30.** Methyllithium (3.25 mL, 5 mmol, 1.4 M ether) was added to a solution of Compound 1 (1.22 g, 4 mmol) at -70°C . After 10 min n-BuLi (1.6 M in hexanes, 2.83 mL, 5 mmol) was added and stirred for 30 min. A solution of Compound 29 (1.44g, 4.55mmoles), dissolved in THF (15mL) was added. The resulting mixture was stirred at -70°C for 2.5 h, quenched with water, warmed to 0°C and then
- 10 extracted with 2 X 50 mL EtOAc. The organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated to an oil. Purification by sgc (EtOAc : hexanes) gave Compound 30 (1.4 g, 58%) as a gum.

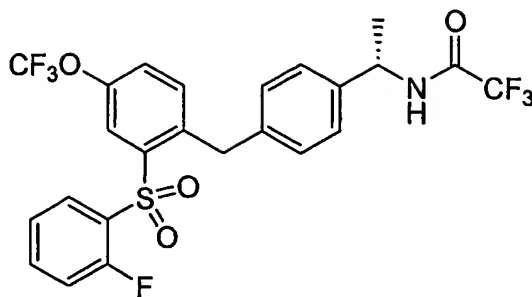


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Compound 31

- 20 **Compound 31.** Triethylsilane (3.5 mL, 22.5 mmol) was added to a solution of Compound 30 (0.6 g ,1.125 mmol) in CH_2Cl_2 (30 mL), followed by addition of boron trifluoride etherate (0.32 mL, 1.94 mmol). After stirring at rt for 15 min the reaction mixture was diluted with 50 mL CH_2Cl_2 , washed with water, dried over Na_2SO_4 , filtered, and concentrated to give a solid. Purification via PTLC (25%EtOAc/hexanes (1:3) gave Compound 31 (0.47 g, 89 %) as a solid.

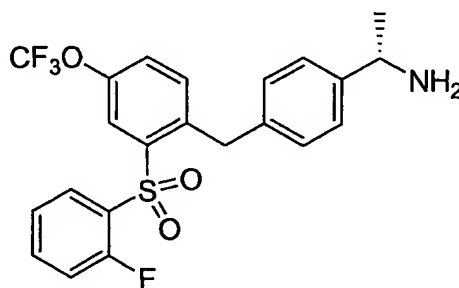
- 70 -



Compound 32

5 **Compound 32.** MCPBA (1.56 g (56%), 5.09 mmol) was added to a solution of Compound 31 (0.47 g, 0.9 mmol) in CH₂Cl₂ (30 mL) at rt. After stirring for 16 h the reaction was washed with 5% aq NaHSO₃, aq NaHCO₃, and water. The organics were dried over Na₂SO₄, filtered, and concentrated to give Compound 31 (0.4 g, 82%) as a solid.

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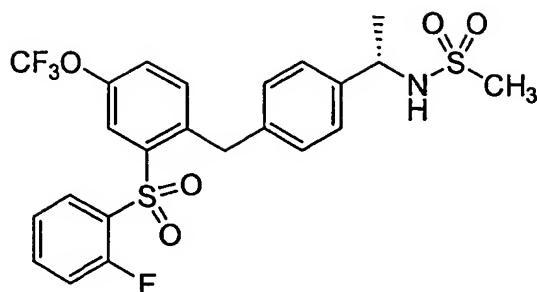


Compound 33

15 **Compound 33.** 1 M aq LiOH (9.7 mL, 9.7 mmol) was added to a solution of Compound 32 (1.78 g, 3.2 mmol) in 1,4-dioxane (15 mL). The resulting mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in 50 mL CH₂Cl₂ and washed with 10 mL brine. The organics were dried over Na₂SO₄, filtered and concentrated to an oil, which was used in the next step

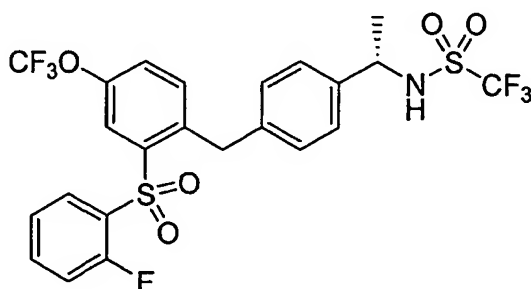
20 without additional purification.

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Compound 34

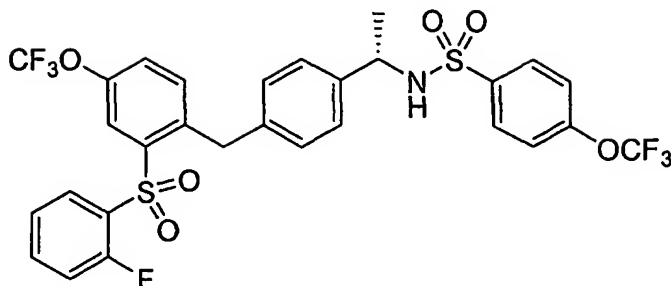
- 5 **Compound 34.** Triethylamine (0.28 mL, 2 mmol) was added to a solution of Compound 33 (0.18 g, 0.4 mmol) in CH_2Cl_2 at rt, followed by addition of MsCl (0.061 mL, 7.9 mmol) in 0.2 mL CH_2Cl_2 . The mixture was stirred overnight, then washed with 2 X 10 mL water, dried over Na_2SO_4 , filtered, and concentrated to give an oil. The oil was purified via PTLC using EtOAc : hexanes (1:1) as the solvent to give Compound
- 10 34 (0.137g, 65%) as a solid.



Compound XIX

- 15 **Compound XIX.** Triethylamine (0.296 mL, 2.1 mmol) was added to a solution of Compound 33 (0.4 g, 0.9 mmol) in 8 mL of CH_2Cl_2 , cooled to 0°C , followed by addition of a solution of trifluoromethanesulfonic anhydride (0.54 g, 1.9 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0°C for 3 h, washed with water, dried over
- 20 Na_2SO_4 , filtered, concentrated under reduced pressure to give crude Compound XIX. The crude product was purified via PTLC using 33% EtOAc:hexanes to give Compound XIX as a solid (0.32 g, 62%).

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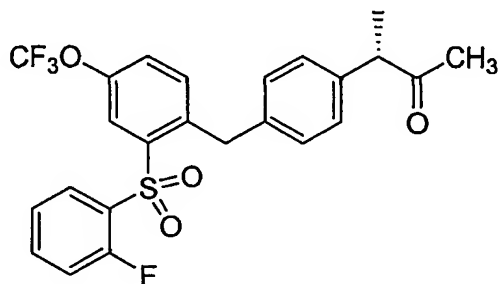
EXAMPLE XIV

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Compound XX

Compound XX. Triethylamine (0.018 mL, 0.129 mmol) was added to a solution of Compound 33 (0.05 g, 0.11 mmol) in CH₂Cl₂ (1.5 mL) followed by addition of 4-(trifluoromethoxy)benzenesulfonyl chloride (0.02 mL, 0.118 mmol) in CH₂Cl₂ at rt. The stirring was continued for 10 h. The reaction mixture was diluted with 50 mL CH₂Cl₂, washed with water, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by PTLC (33%EtOAc: hexanes to give Compound XX as a solid (0.048 g, 65%).

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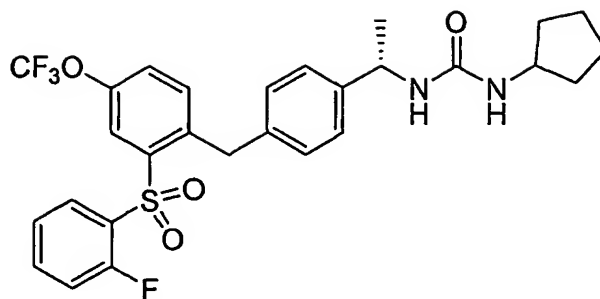


Compound XXI

Compound XXI. Triethylamine (0.012 mL, 0.086 mmol) was added to a solution of Compound 33 (0.033 g, 0.073 mmol) in CH₂Cl₂ (1 mL) at -5 °C. A solution of acetyl chloride (0.0057 mL, 0.08 mmol) in 0.5 mL CH₂Cl₂ was added. The mixture was stirred overnight at rt. The organics were washed with water, and then dried over Na₂SO₄, filtered, and then concentrated under reduced pressure. The resulting crude was purified by PTLC (EtOAc) to provide Compound XXI as a solid (0.009 g, 25%).

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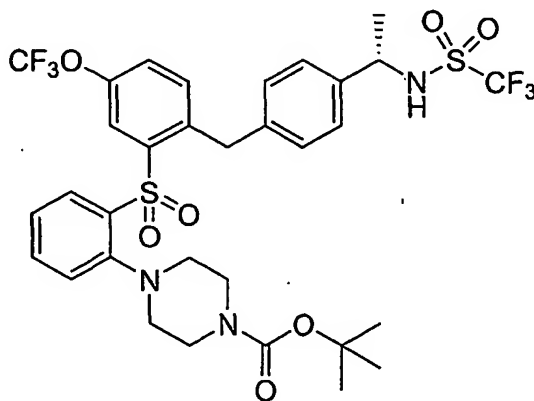
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Compound XXII

5 **Compound XXII.** Cyclopentyl isocyanate (0.0135 g, 0.12 mmol) was added as a CH_2Cl_2 solution (0.5 mL) to a solution of Compound 33 (0.05 g, 0.11 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the crude product was subjected to PTLC (EtOAc/hexanes 1:2) to provide Compound XXII (0.04 g, 65%).

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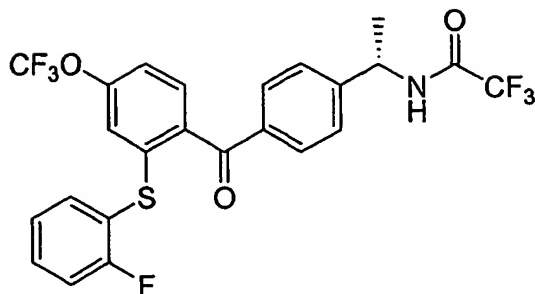
EXAMPLE XV

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Compound XXIII

20 **Compound XXIII.** N-Boc-piperazine (0.5 g, 2.68 mmol) was added to a solution of Compound XIX (0.2 g, 0.34 mmol) in CH_3CN (10 mL). The reaction was heated at 80°C for 72 h. Additional N-Boc-piperazine (0.25 g, 1.34 mmol) was added and heated at 80°C for another 16 h. The solvent was removed under reduced pressure and the crude product was purified via PTLC (50%EtOAc:hexanes) to provide Compound XXIII as a solid, (0.096 g, 37%).

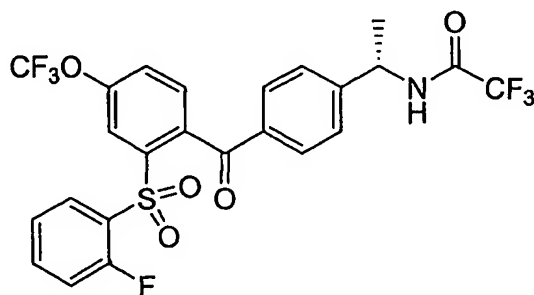
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EXAMPLE XVI

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Compound 35

Compound 35. Pyridinium chlorochromate (0.194 g, 0.899 mmol) was added to a mixture of Compound 30 (0.4 g, 0.75 mmol) and Celite (0.4 g) in CH_2Cl_2 (10 mL) at rt. The mixture was stirred for 18 h, filtered through Celite and concentrated. The crude material was purified via PTLC using 33% EtOAc:hexanes to obtain Compound 35 (0.4 g, 100%).

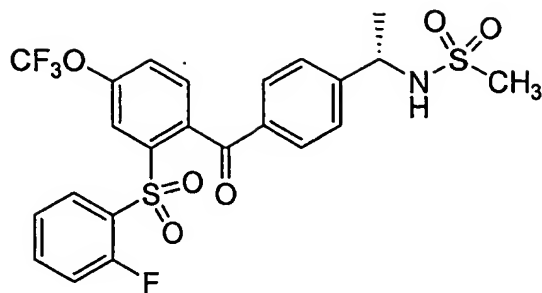


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Compound 36

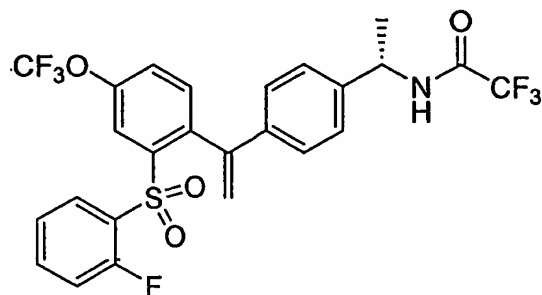
Compound 36. MCPBA (1.29 g (56%), 4.18 mmol) was added to a solution of Compound 35 (0.4 g, 0.75 mmol) in CH_2Cl_2 (20 mL) and stirred at rt for 18 h. The reaction was washed with 5% aq NaHSO_3 , 5% NaHCO_3 , and water. The organics were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified via PTLC using EtOAc:hexanes (1:1) to provide Compound 36 (0.34 g, 80%).

- 75 -



Compound 37

- 5 **Compound 37.** Compound 36 was converted to Compound 37 using a procedure similar to that described in example II.



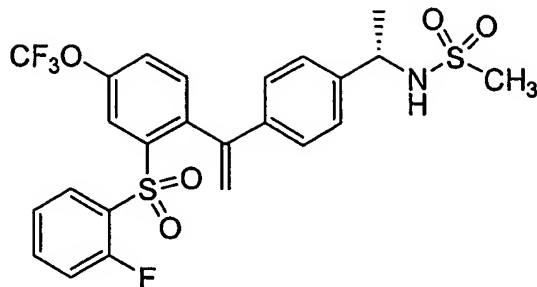
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Compound 38

- 15 **Compound 38.** LHMDs (0.9 mL, 1M solution THF, 0.896 mmol) was added to a suspension of methyltriphenylphosphonium bromide (0.215 g, 0.6 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min, then for 10 minutes at rt. A solution of Compound 36 (0.17 g, 0.3 mmol) in THF (8mL) was added and stirring continued for 10 h at rt. The mixture was diluted with EtOAc and washed with water. The organics were dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified via PTLC using EtOAc:hexanes (1:3) to provide Compound 38 as a solid. (0.09 g, 54%).

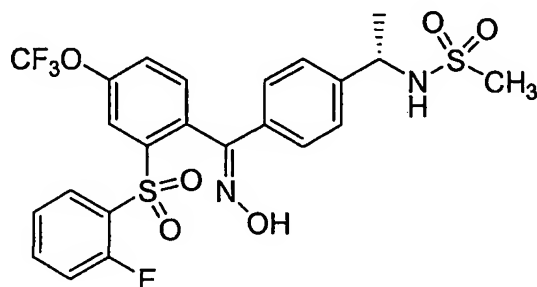
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Compound XXIV

- 5 **Compound XXIV.** Compound 38 was converted to Compound XXIV using a procedure similar to that described in example II.

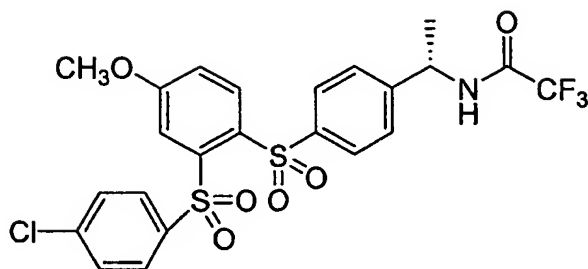


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Compound XXV

- 15 **Compound XXV.** Hydroxylamine hydrochloride (0.076 g, 1.09 mmol) was added to a solution of Compound 37 (0.03 g, 0.055 mmol) in pyridine (0.5 mL). The mixture was heated at 80 °C for 24 h. The mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in 50 mL CH₂Cl₂ and washed with water and brine. The organics were dried over Na₂SO₄, filtered and concentrated to provide crude Compound XXV, which was purified via PTLC (EtOAc/hexanes, 1:3) to afford Compound XXV as a solid (0.01 g, 33%).

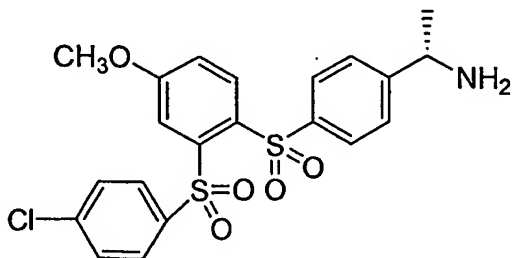
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EXAMPLE XVII

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Compound 39

Compound 39. In a flame dried flask under N₂ blanket, Compound 2 (4.00 g, 10.32 mmol) was dissolved in anhyd THF (41 mL) and cooled to -78°C. A solution of n-BuLi (2.5 M in hexanes, 8.25 mL, 20.6 mmol) was added and the reaction mixture was stirred for 25 min. Bis-4-chlorophenyl disulfide (3.10 g/ 10.8 mmol) was added and the reaction mixture was stirred at -78°C for 3 h then between -78 °C and -10°C for 3 h. The reaction mixture was quenched with pH 7.0 sodium phosphate buffer (1.0 M, 50 mL). The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, then dried with Na₂SO₄ and concentrated to dryness. The crude product (5.44 g foam) was dissolved in CH₂Cl₂ (120 mL) and cooled to 0°C. MCPBA (7.24 g) was added. The ice bath was removed and the reaction mixture was stirred at rt overnight. Aqueous NaHCO₃ and CH₂Cl₂ were added and the layers were separated. The organic layer was washed with aq NaHSO₃, NaHCO₃, H₂O, and brine then dried with MgSO₄. The crude product was purified by sgc (35%-40% EtOAc/hexanes gradient) to give 1.86 g (32%) of Compound 39.



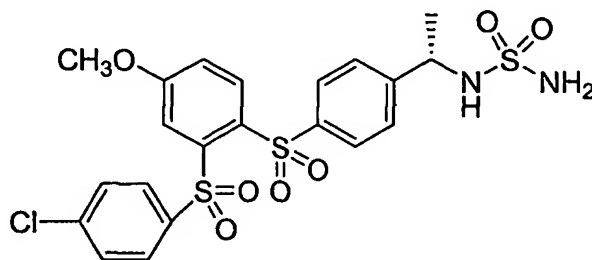
Compound 40

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Compound 40. Compound 39 (1.52 g, 2.70 mmol) was dissolved in dioxane (9 mL) and cooled to 0°C. LiOH (1.0 M aq, 3 mL, 3 mmol) was added and the reaction mixture was left stirring overnight, during which time it warmed to rt. The solvents were evaporated. CH₂Cl₂ and aq NaOH were added and the layers were separated.

- 5 The aqueous layer was extracted with additional CH₂Cl₂ and the combined organic layer was dried with Na₂SO₄ and concentrated to give 0.85 g (68%) of Compound 40.



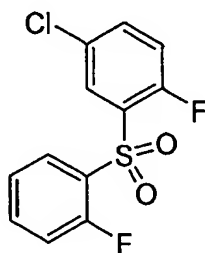
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Compound XXVI

Compound XXVI. Compound 40 (143 mg, 0.307 mmol) was dissolved in dioxane and sulfamide (0.128, 1.33 mmol) was added. The reaction mixture was stirred at reflux for 24 h then allowed to cool to rt and concentrated. The reaction mixture was purified via PTLC (5% MeOH/CH₂Cl₂) giving 54 mg (32%) of Compound XXVI.

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Example XVIII



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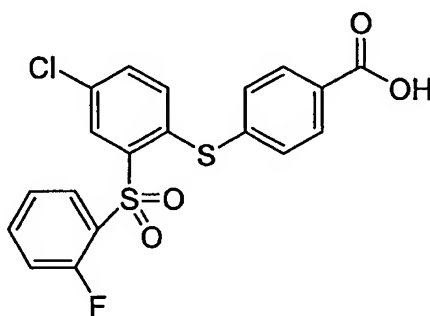
Compound 41

Compound 41. In a flame dried flask under N₂ blanket, 1-chloro-4-fluorobenzene (7.36 g, 56.4 mmol) was dissolved in anhyd THF and cooled in a dry ice/acetone bath. n-BuLi (2.5 M in hexanes, 22.5 mL, 56.3 mmol) was added and the

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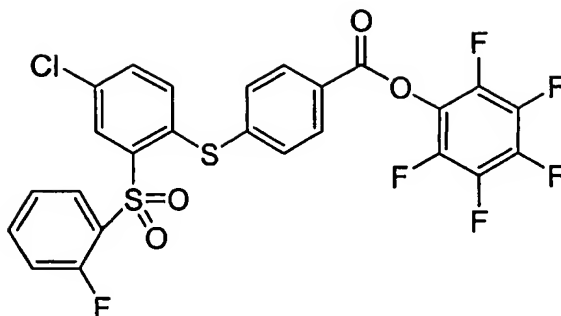
reaction was stirred for 50 min. 2-Fluorobenzene sulfonyl fluoride (10.3 g, 57.8 mmol) was added and the reaction mixture was left stirring overnight, during which time it warmed to rt. Saturated aq NH_4Cl (100 mL) was added, followed by EtOAc (100 mL) and the layers were separated. The organic layer was washed with water and brine, then dried with MgSO_4 . The solvents were evaporated and the crude product was purified via sgc (10% EtOAc/hexanes) to afford Compound 41 (2.55 g, 16%) as a solid.



Compound 42

Compound 42. 4-Mercaptobenzoic acid (0.54 g, 3.50 mmol) was dissolved in DMA (10 mL) and cooled in an ice bath. Sodium hydride (60% suspension in oil, 0.30 g, 7.5 mmol) was added and the reaction mixture was stirred for 20 min. The ice bath was removed and the reaction mixture was stirred for 1 h. The flask was cooled to 0°C again and compound 41 (1.0 g, 3.46 mmol) dissolved in DMA (5 mL) was added. The reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to rt and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% aq HCl, water, and brine. The organic layer was dried with Na_2SO_4 and the solvents were evaporated. The crude product was purified via sgc (5% MeOH/ CH_2Cl_2) to give Compound 42 as a solid (1.04 g, 71%).

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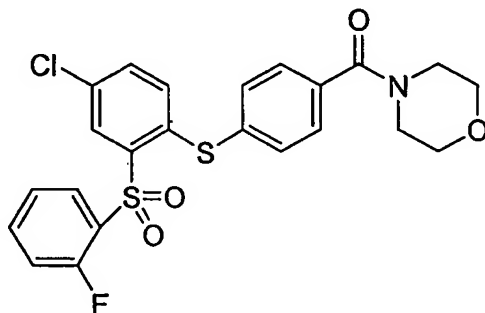


Compound 43

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Compound 43. Pentafluorophenol (0.91 g, 4.94 mmol) and Compound 42 (1.04 g, 2.46 mmol) were dissolved in 30 mL of CH₂Cl₂ and EDCI was added. The reaction was stirred overnight and diluted with water and CH₂Cl₂. The layers were separated and the organic layer was washed with water and dried with Na₂SO₄. The crude product was purified via sgc (5% EtOAc/hexanes) to give 0.9 g (62%) of Compound 43 as a solid.

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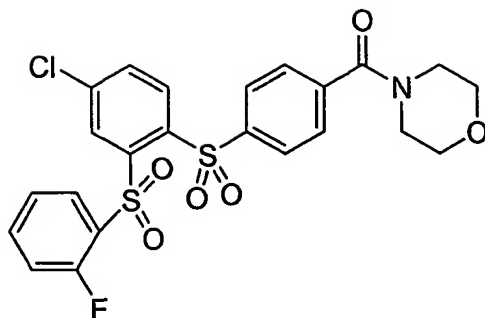
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Compound XXVII

Compound XXVII. Compound 43 (0.15 g, 0.25 mmol) was dissolved in CH₂Cl₂ (5 mL). Morpholine (44 mg, 0.51 mmol) and DIPEA (49 mg, 0.38 mmol) were added and the reaction mixture was stirred at rt for 2h. The reaction mixture was diluted with EtOAc and washed with 5% aq NaHCO₃, water and brine. The organic layer was dried with Na₂SO₄ and the solvents were evaporated. The crude product was purified via sgc (50% EtOAc/hexanes) to give 98 mg (77%) of Compound XXVII.

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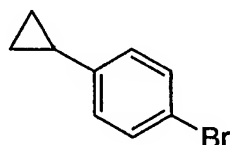
- 81 -



Compound XXVIII

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Compound XXVIII. Compound XXXVII (72 mg, 0.146 mmol) was dissolved in CH_2Cl_2 (3 mL) and MCPBA (ca 50%, 0.11 g, ca 0.36 mmol) was added. The reaction mixture was stirred overnight then diluted with CH_2Cl_2 . The reaction mixture was washed with aq Na_2CO_3 and water then dried with Na_2SO_4 . The solvents were
10 evaporated and the crude product was purified via sgc (60% EtOAc/hexanes) to give 61 mg (79%) of Compound XXXVIII as a solid.

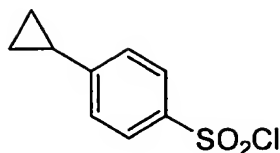
Example XIX

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Compound 44

Compound 44. Cyclopropyl benzene (48.5 g, 410 mmol), glacial acetic acid
20 (510 mL), and sodium acetate (38.9 g, 474 mmol) were added to a roundbottomed flask. The flask was cooled in an ice-water bath. A solution of bromine (66.3 g, 414 mmol) dissolved in 105 mL of acetic acid was added dropwise over 90 min. The reaction mixture was stirred at temperatures between 0 °C and 10 °C for 5 h. The reaction was then allowed to warm to rt overnight. Hexanes (1300 mL) and water
25 (250 mL) were added. Aqueous NaHSO_3 (1M) was added until the reaction mixture changed from yellow to clear. The layers were separated. The organic layer was washed with water, 1M aq Na_2CO_3 , and brine, then dried with Na_2SO_4 . The solvent was evaporated and the crude product was purified via sgc using hexanes as the mobile phase to give 17 g of p-cyclopropylbromobenzene (21%) (Compound 44).

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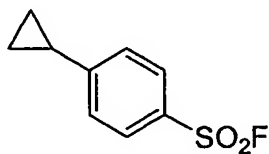
Compound 45

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Compound 45. A flask was flame dried under N₂ blanket. Compound 44 (10.0 g, 50.7 mmol) was added, followed by dry THF (100 mL). The resulting solution was cooled to -78 °C. A solution of n-butyl lithium in hexanes (2.27 M, 22.35 mL, 50.7 mmol) was added dropwise *via* syringe. The reaction mixture was stirred for 10 min.

- 10 SO₂ gas was bubbled into the reaction mixture until the pH of a reaction mixture sample was <1 when mixed with water. The reaction mixture was stirred for 30 min at -78 °C. The ice bath was removed and the reaction mixture was allowed to warm to rt. The reaction mixture was stirred for an additional 30 min at rt. The reaction mixture was concentrated to afford a solid. CH₂Cl₂ (500 mL) and N-
- 15 chlorosuccinamide (10.2 g, 76 mmol) were added and the reaction mixture was stirred for 4 hrs at rt. Water and CH₂Cl₂ were added and the layers were separated. The organic layer was washed with water and brine, then dried with MgSO₄. The solution was filtered and the solvents were evaporated to give 13.3 g of crude p-cyclopropylbenzenesulfonyl chloride (Compound 45).

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Compound 46

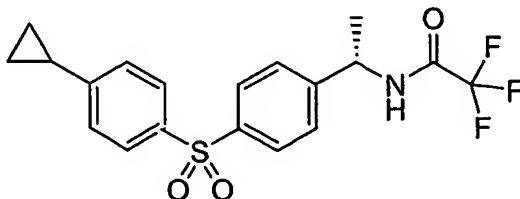
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Compound 46. Crude compound 45 (13.3 g) was dissolved in 200 mL of acetone and 60 mL of water. Potassium fluoride (7.12 g, 122 mmol) was added and the reaction mixture was stirred overnight at rt. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried with Na₂SO₄, filtered, and

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concentrated to dryness to give 9.80 g (97%) of crude p-cyclopropyl benzenesulfonyl fluoride (Compound 46).

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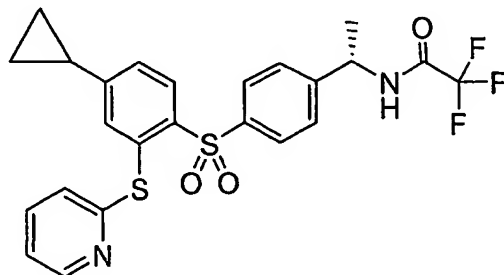


Compound 47

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Compound 47. A flask was flame dried under N₂ blanket. Compound 1 (44.29 g, 150 mmol) was added, followed by 500 mL of anhydrous THF. The flask was cooled to -78 °C and a solution of n-butyl lithium in hexanes (1.77 M, 154 mL, 272 mmol) was added over 40 min. The reaction mixture was stirred for 1.5 h at -78 °C, then transferred *via* cannula into a solution of crude p-cyclopropylbenzenesulfonyl fluoride (27.2 g, 135 mmol) dissolved in 200 mL of anhydrous THF over 1.5 h. The reaction mixture was stirred for 1h. Water was added, followed by EtOAc. The layers were separated and the organic layer was washed with aq NH₄Cl, water, and brine, then dried with Na₂SO₄. The solvents were evaporated, and the crude product was purified by sgc (25%-33% EtOAc/Hexanes gradient mobile phase) to give 24.5 g (45%) of compound 47.

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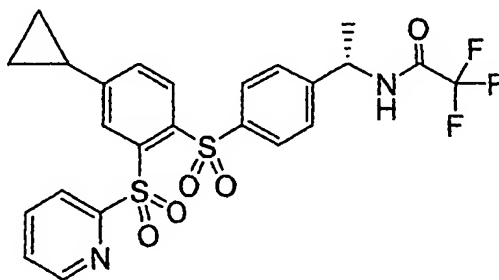


Compound 48

Compound 48. A flask was flame dried under N₂ blanket. Compound 47 (16.33 g, 41.1 mmol) was dissolved in 400 mL of anhydrous THF and cooled to -78

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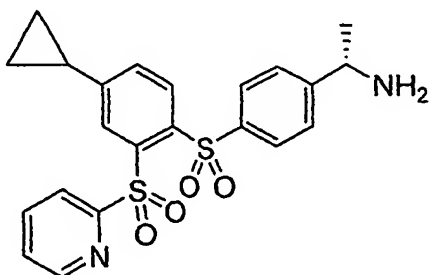
°C. A solution of n-butyl lithium in hexanes (2.3 M, 35.7 mL, 82.1 mmol) was added dropwise *via* syringe. The reaction mixture was stirred for 1.5 h at -78 °C. A solution of 2, 2'-dithiodipyridine (8.89 g, 41.1 mmol) dissolved in 40 mL of THF was added and the reaction mixture was stirred for 2 h. The cold bath was removed, and the reaction mixture was allowed to warm to rt overnight. The reaction mixture was cooled with an ice-water bath and the reaction was quenched with 10 mL of water. The reaction mixture was diluted with EtOAc and washed with saturated aq NH₄Cl, water, and brine. The organic layer was dried with Na₂SO₄ and concentrated. The crude product was purified *via* sgc using 1:2 EtOAc/Hexanes as the mobile phase giving 15.49 g (74%) of Compound 48.



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Compound 49

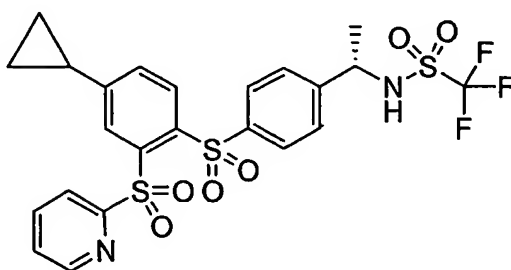
Compound 49. Compound 48 (15.49 g, 30.6 mmol) was dissolved in 1 L of CH₂Cl₂ and the flask was placed in a rt water bath. MCPBA (22.0 g, ca 74 mmol) was added in portions and the reaction mixture was left stirring overnight at rt. The reaction mixture was diluted with CH₂Cl₂ and washed with 10% aq NaHCO₃, water, and brine, then dried with Na₂SO₄. The solvent was evaporated and the crude product was purified *via* sgc using a 20%-50% EtOAc/Hexanes gradient as the mobile phase. Compound 49 (9.4 g, 57%) was isolated as a solid.



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Compound 50

Compound 50. Compound 49 (10.16 g, 18.87 mmol) was dissolved in 300 mL of p-dioxane and 300 mL of 1.0 M aq LiOH was added. The reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with CH₂Cl₂. The layers were separated, and the organic layer was washed with water and brine, then dried with Na₂SO₄. The solvents were evaporated to give 9.0 g of crude Compound 50.

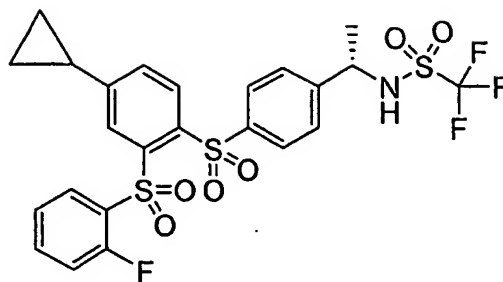


Compound XXIX

Compound XXIX. Crude compound 50 (7.74 g, 17.5 mmol) was dissolved in CH₂Cl₂ (250 mL). Diisopropylethylamine (2.71 g, 21 mmol) was added and the flask was cooled to -78 °C. A solution of triflic anhydride (5.97 g, 21.1 mmol) dissolved in CH₂Cl₂ (50mL) was added dropwise over 1h. The reaction mixture was stirred for 2 h at -78 °C. The cold bath was removed, and the reaction mixture was allowed to warm to rt overnight. The reaction mixture was diluted with CH₂Cl₂ and washed with water and brine. The organic layer was dried with Na₂SO₄ and the solvents were evaporated. The crude product was purified *via* sgc using 1:2 EtOAc/Hexanes as the mobile phase to give 8.61 g (85%) of Compound XXIX.

Compound XXIX: ¹H NMR (300 MHz, CDCl₃): δ 8.56-8.52 (m, 1H), 8.32-8.21 (m, 3H), 8.02-7.92 (m, 4H), 5.42 (d, 9 Hz, 1H), 8.02-7.92 (m, 4H), 5.42 (d, 1H, 9 Hz), 4.84-4.78 (m, 1H), 2.16-2.06 (m, 1H), 1.60 (d, 7Hz, 3H), 1.20-1.17 (m, 2H), 0.97-0.89 (m, 1H).

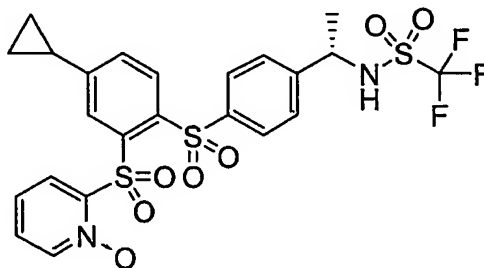
- 86 -



Compound XXX

- 5 **Compound XXX.** Compound XXX was prepared from compound 47 using the procedures in example II.

Compound XXX: ^1H NMR (300 MHz, CDCl_3): δ 8.33-8.22 (m, 3H), 8.00-7.94 (m, 2H), 7.66-7.58 (m, 1H), 7.53-7.37 (m, 4H), 7.16-7.05 (m, 1H), 5.160 (d, 9 Hz, 1H), 4.88-4.83 (m, 1H), 2.17-2.06 (m, 1H), 1.65 (d, 7 Hz, 3H), 1.28-1.20 (m, 2H), 0.97-0.90 (m, 2H).



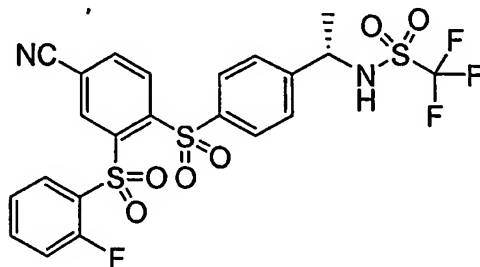
Compound XXXI

- 15 **Compound XXXI.** The potassium salt of compound XXIX (56 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (5 mL) and Na_2HPO_4 (0.13 g, 0.91 mmol), and urea-hydrogen peroxide complex (85 mg, 0.90 mmol) were added. Trifluoroacetic acid was added (47 mg, 0.22 mmol) and the reaction mixture was refluxed for 4 h then left stirring overnight at rt. Additional urea-hydrogen peroxide complex (85 mg, 0.9 mmol) and TFAA (0.56 mmol) were added and the reaction mixture was refluxed for 6h. The reaction mixture was allowed to cool to rt and diluted with CH_2Cl_2 and water. The layers were separated and the organic layer was washed with water, dried with Na_2SO_4 , and concentrated. The crude product was purified *via* PTLC on silica using EtOAc as the mobile phase to give 34 mg (64%) of compound XXXI.

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Compound XXXI: ^1H NMR (300 MHz, CDCl_3): δ 8.38-8.29 (m, 2H), 8.17 (d, 8 Hz, 1H), 8.07-8.02 (m, 1H), 7.91-7.85 (m, 2H), 7.56-7.36 (m, 5H), 6.11 (d, 8 Hz, 1H), 4.84-4.78 (m, 1H), 2.12-2.01 (m, 1H), 1.57 (d, 7Hz, 3H), 1.21-1.12 (m, 2H), 0.92-0.86 (m, 2H).

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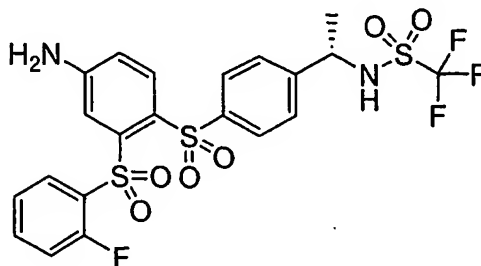


Compound XXXII

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Compound XXXII. Compound V (0.50 g, 0.85 mmol), zinc (II) cyanide (65 mg, 0.55 mmol), zinc dust (11 mg, 0.17 mmol), 1,1'-Bis(diphenylphosphino)ferrocene (21 mg, 0.04 mmol), and tris(dibenzylideneacetone) dipalladium (17 mg, 0.129 mmol) were added to a 25 mL flask. Dimethylacetamide was added and the reaction mixture was placed under N_2 blanket and heated to 110 $^\circ\text{C}$. The reaction mixture was stirred at 110 $^\circ\text{C}$ for 4 h, then partitioned between EtOAc and water. The organic layer was washed with 2M ammonium hydroxide, water, and brine, then dried with MgSO_4 . Evaporation of the solvent afforded 0.49 g of an oil that was purified *via* sgc using a 20%-25% EtOAc/Hexanes gradient mobile phase to afford compound XXXII (0.20 g).

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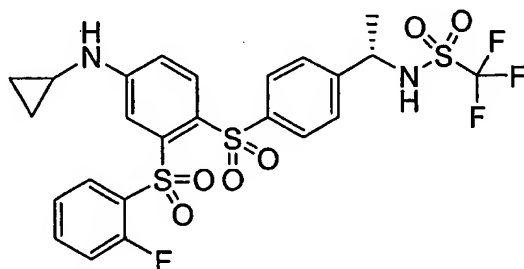
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Compound XXXIII

Compound XXXIII. Compound V (0.51 g, 0.87 mmol), tris(dibenzylideneacetone) dipalladium (40 mg, 0.04 mmol), 2-(dicyclohexylphosphino)-

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biphenyl (36 mg, 0.103 mmol), and sodium tert-butoxide (204 mg, 2.12 mmol) were added to a Schlenck flask under N₂ blanket. Toluene (2.5 mL) was added, followed by benzophenone imine (210 mg, 1.15 mmol). The reaction mixture was stirred overnight at 70 °C under N₂. The reaction mixture was allowed to cool to rt and 1 M aq HCl was added. The reaction mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with water and brine, then dried with MgSO₄. The resulting material was filtered and concentrated to give 0.37 g of an oil. The crude product was purified *via* sgc using a 25%-50% EtOAc/Hexanes gradient mobile phase, followed by a 5%MeOH/45%EtOAc/50%Hexanes mobile phase to give 0.11 g of an oil as product.

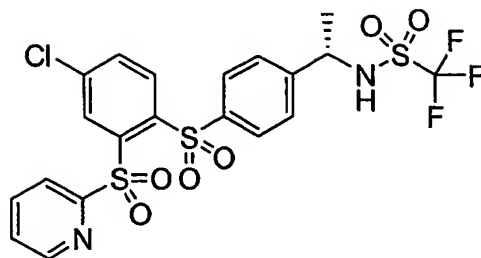


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Compound XXXIV

Compound XXXIV. Compound V (264 mg, 0.45 mmol), sodium tert-butoxide (103 mg, 1.07 mmol), tris(dibenzylideneacetone) dipalladium (107 mg, 0.116 mmol), and 2-(di-tert-butyl-phosphino)biphenyl (61 mg, 0.20 mmol) were added to a Schlenck flask under N₂. THF (1.5 mL) and cyclopropylamine (0.6 g, 10.5 mmol) were added and the reaction mixture was stirred for 24 h at rt. EtOAc and 1 M aq HCl were added and the layers were separated. The organic layer was washed with 1 M aq HCl, water, and brine, then dried with MgSO₄. Filtration and evaporation of the solvents gave an oil which was purified *via* sgc using 25% EtOAc/Hexanes as the mobile phase. Compound XXIV (109 mg) was obtained as a foam.

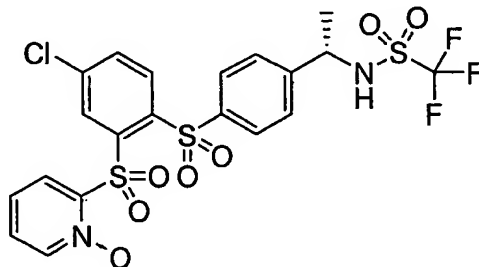
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**Compound XXXV**

5 **Compound XXXV.** Compound XXXV was prepared from compound 5 according to the procedures in Example XIX.

Compound XXXV: ¹H NMR (300 MHz, CDCl₃): δ 8.88 (d, 1.2 Hz, 1H), 8.51-8.56 (m, 2H), 8.31 (dd, 8 Hz, 1 Hz, 1H), 8.18 (dd, 8 Hz, 1 Hz, 1H), 8.08-7.96 (m, 3H), 7.62-7.48 (m, 3H), 5.51 (d, 9Hz, 1H), 4.90-4.70 (m, 1H), 1.62 (d, 7 Hz, 3H).

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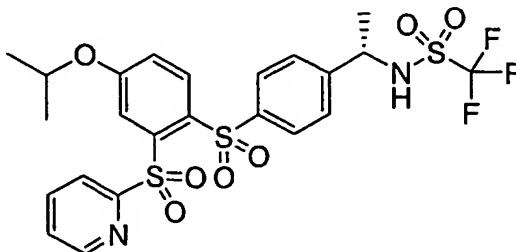
Compound XXXVI

Compound XXXVI. Compound XXXVI was prepared from compound XXXV according to the procedure in Example XIX.

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Compound XXXVI: ¹H NMR (300 MHz, CDCl₃): δ 10.19 (d, 7.8 Hz, 1H), 8.27-8.42 (m, 4H), 8.13 (dd, 7.8 Hz, 2.1 Hz, 1H), 7.93 (d, 8.4 Hz, 2H), 7.78-7.63 (m, 2H), 7.59 (d, 8.4 Hz, 2H), 4.80 (m, 1H), 1.44 (d, 6.9 Hz, 3H).

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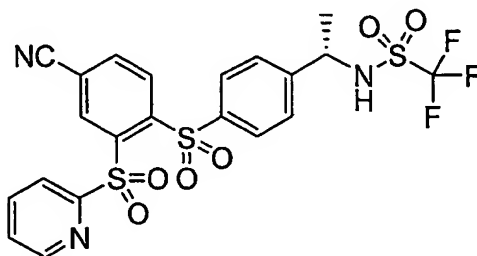


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Compound XXXVII

Compound XXXVII. Compound XXXV (0.312 g, 0.548 mmol) was dissolved in
5 2 propanol (20 mL) and 1.0 M aq NaOH was added (10 mL). The reaction mixture
was stirred at temperatures between 80 °C to 84 °C for six days. The reaction mixture
was allowed to cool to rt and partially concentrated. EtOAc was added and the layers
were separated. The aqueous layer was acidified with 1 M aq H₂SO₄ and extracted
with EtOAc. The combined organic layer was dried with MgSO₄ and concentrated to
10 give 0.29 g of an oil. The crude product was purified via sgc using a 25%-33%
EtOAc/Hexanes gradient as the mobile phase. The fraction containing Compound
XXVII was repurified via sgc using 3% MeOH/CH₂Cl₂ as the mobile phase to give
0.05 g (15%) of Compound XXXVII as a solid.

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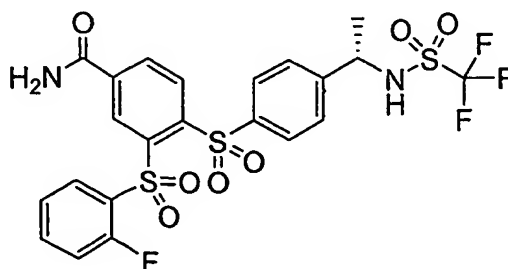


Compound XXXVIII

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Compound XXXVIII. Compound XXXVIII was prepared from compound XXXV
according to the procedure used to prepare compound XXXII.

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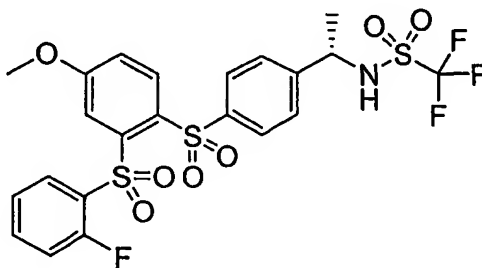


Compound XXXIX

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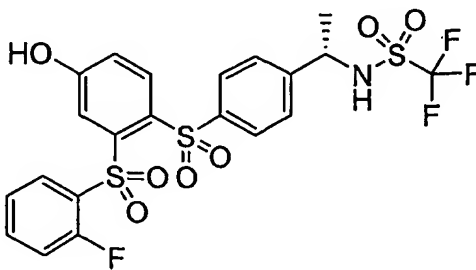
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Compound XXXIX. Compound XXXII (0.10 g, 0.17 mmol) was dissolved in acetone (1.5 mL) and water (1 mL). Potassium carbonate (3 mg, 0.022 mmol) and urea-hydrogen peroxide complex (0.16 g, 1.70 mmol) were added and the reaction mixture was stirred overnight at rt. The reaction mixture was diluted with EtOAc and washed with water. The solvents were evaporated and the crude product was purified via PTLC on SiO₂ using 50% EtOAc/Hexanes as the mobile phase to afford
5 Compound XXXIX (75 mg, 73%) as a solid.



Compound XXXX

15 **Compound XXXX.** Compound XXXX was prepared from compound 2 according to the procedures in Example II.

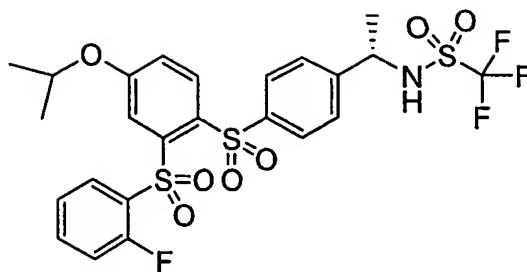


Compound XXXXI

Compound XXXXI. Compound XXXXI was prepared from compound XXXX according to the procedure used to convert compound 16 to compound X.

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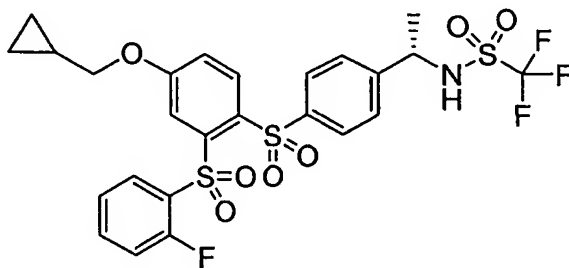


Compound XXXXII

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Compound XXXXII. Compound XXXXI (0.15 g, 0.264 mmol) was dissolved in DMA (5 mL). Potassium iodide (0.22 g, 1.30 mmol), cesium carbonate (0.19 g, 0.58 mmol), and 2-bromopropane (49 mg, 0.398 mmol) were added and the reaction mixture was left stirring at rt over the weekend. EtOAc was added and the reaction mixture was washed with satd. aq NH₄Cl and water. The organic layer was dried with Na₂SO₄ and concentrated. The crude product was purified *via* sgc using 3% Et₂O/CH₂Cl₂ as the mobile phase to give 83 mg (51%) of Compound XXXXII.

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Compound XXXXIII

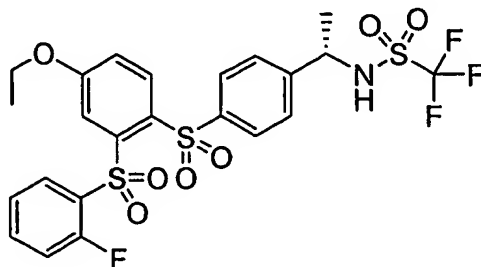
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Compound XXXXIII. Compound XXXXI (0.10 g, 0.176 mmol) was dissolved in DMF (2 mL). Sodium hydride (7 mg, ca 1.2 eq) and bromomethylcyclopropane (26 mg, 0.19 mmol) were added and the reaction was stirred at 50 °C for 4 hr then allowed to cool to rt. EtOAc and water were added, and the layers were separated. The organic layer was washed with water and dried with Na₂SO₄. The solvent was

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evaporated and the crude product was purified via sgc using 33% EtOAc/Hexanes as the mobile phase to give 15 mg (14%) of Compound XXXXIII.

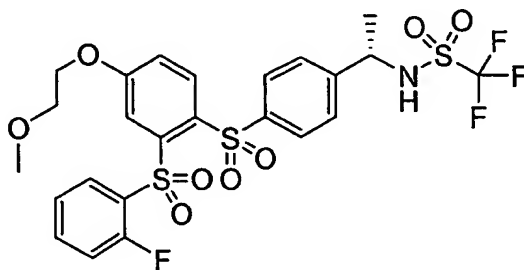


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Compound XXXXIV

Compound XXXXIV. Compound XXXXIV was prepared according to the procedure used for Compound XXXXIII using ethyl iodide as the electrophile and stirring the reaction at rt overnight before workup.

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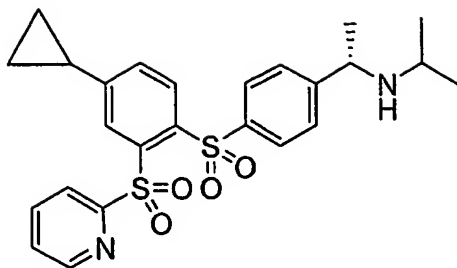
Compound XXXXV

Compound XXXXV. Compound XXXXI (0.40 g, 0.70 mmol) was dissolved in DMF (8 mL) and NaH (62 mg, ca 2.2 eq) was added. The reaction mixture was stirred for 30 min. Sodium iodide (0.52 g, 3.46 mmol) and 2-chloroethyl methyl ether (80 mg, 0.85 mmol) were added. The reaction mixture was stirred for 1 h at rt then 5 h at 110 °C. The reaction mixture was allowed to cool to rt. EtOAc and satd aq NH₄Cl were added and the layers were separated. The organic layer was washed with water and dried with Na₂SO₄. Evaporation of the solvent, followed by sgc using 50% EtOAc/Hexanes as the mobile phase, afforded 0.21 g (48%) of Compound XXXXV.

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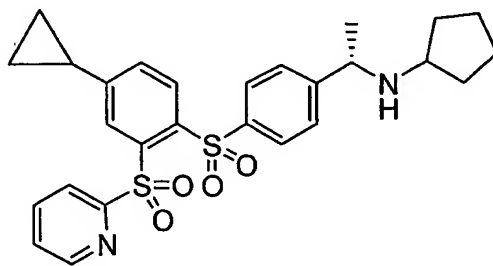
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Compound XXXXVI

- 5 **Compound XXXXVI.** Compound 50 (50 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (3 mL) and acetic acid (7 mg). Acetone (6 mg, 0.13 mmol), and $\text{NaBH}(\text{OAc})_3$ (36 mg, 0.169) were added, and the reaction mixture was left stirring at rt overnight. EtOAc was added and the reaction mixture was washed with 10% Na_2CO_3 and water. The solvents were evaporated and the crude product was purified via PTLC on SiO_2
- 10 using EtOAc as the mobile phase. The resulting product was dissolved in EtOAc and HCl in Et_2O was added causing a white precipitate to form. The solvent was removed and the precipitate was washed with Et_2O and dried *in vacuo* to give 32 mg (49%) of compound XXXXVI as a solid.

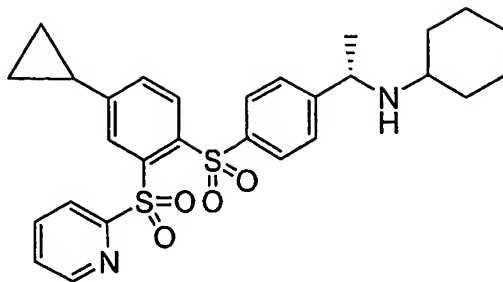
15



Compound XXXXVII

- 20 **Compound XXXXVII.** Compound XXXXVII was prepared according to the procedure used for compound XXXXVI using cyclopentanone as the carbonyl source.

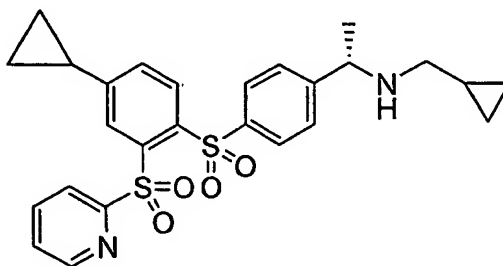
- 95 -



Compound XXXXVIII

5

Compound XXXXVIII. Compound XXXXVIII was prepared according to the procedure used for compound XXXXVI using cyclohexanone as the carbonyl source.

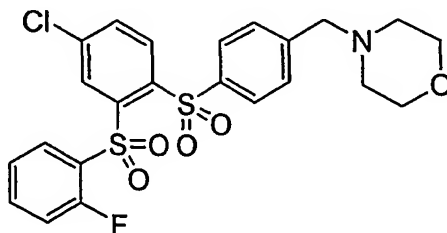


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Compound XXXXIX

Compound XXXXIX. Compound XXXXIX was prepared according to the procedure used for compound XXXXVI using cyclopropanecarboxaldehyde as the carbonyl source.

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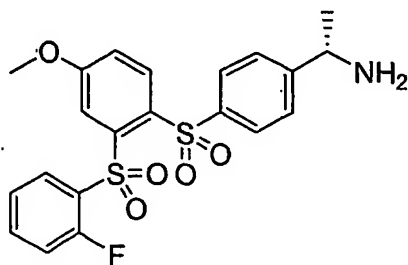


Compound XXXXX

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Compound XXXXX. Compound XXVIII (0.10 g, 0.197 mmol) was dissolved in a solution of borane in THF (1.0 M, 1.0 mL, 1.0 mmol). The reaction mixture was refluxed for 4 h then allowed to cool to rt. The solution was concentrated. Methanol (5 mL) and 1 M aq HCl (5 mL) were added and the resulting solution was stirred for 5 h at rt. The reaction mixture was concentrated and EtOAc was added. The resulting solution was washed with aq NaOH and water, then dried with Na₂SO₄. The solvent was evaporated and the crude product was purified via PTLC using 40% EtOAc/Hexanes as the mobile phase. The product isolated from this step was dissolved in EtOAc, and HCl in Et₂O was added causing a precipitate to form. The solvent was removed and the precipitate was washed with Et₂O and dried *in vacuo* to give 22 mg (21%) of Compound XXXXX as a solid.

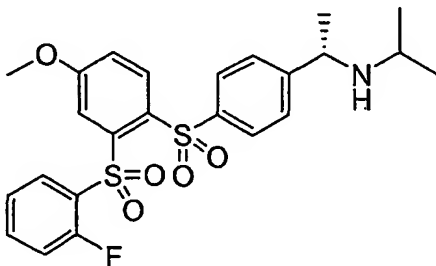


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Compound 51

Compound 51 was prepared from Compound 2 according to the procedures in Example 11.

20

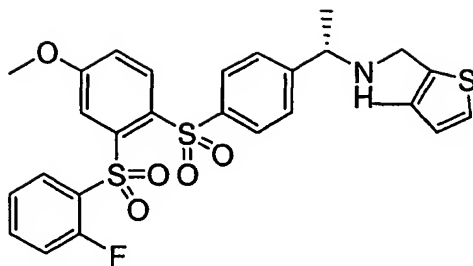


25

Compound XXXXXI

Compound XXXXXI. Compound XXXXXI was prepared from compound 51 according to the procedure used to prepare compound XXXXVI.

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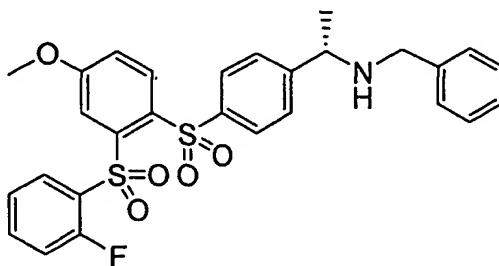


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Compound XXXXXII

Compound XXXXXII. Compound XXXXXII was prepared from compound 51 according to the procedure used to prepare compound XXXXVI using 3-methyl-2-thiophenecarboxaldehyde as the carbonyl source.

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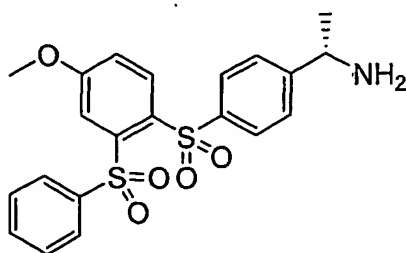


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Compound XXXXXIII

Compound XXXXXIII. Compound XXXXXIII was prepared from compound 51 according to the procedure used to prepare compound XXXXVI using benzaldehyde as the carbonyl source.

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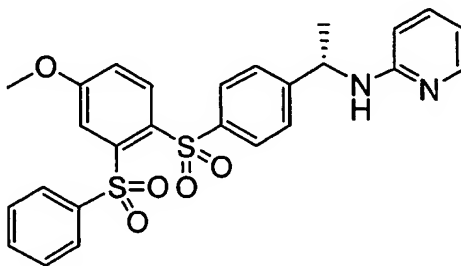
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Compound 52

- 98 -

Compound 52. Compound 52 was prepared from compound 2 using the procedures in Example II with benzenesulfonyl fluoride as the initial electrophile.

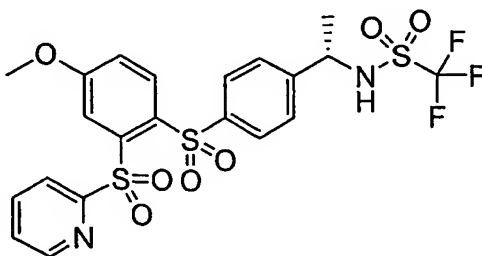
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Compound XXXXIV

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Compound XXXXIV. Compound 52 (0.29 g, 0.67 mmol), cesium carbonate (0.44 g, 1.35 mmol), tris(dibenzylideneacetone) dipalladium (31 mg, 0.034 mmol), dppp (28 mg, 0.068 mmol), and 2-bromopyridine (0.16 g, 1.01 mmol) were dissolved in 11 mL of toluene under N₂ blanket. The reaction mixture was stirred at 80 °C overnight under N₂, then allowed to cool to rt. CH₂Cl₂ was added and the reaction mixture was washed with 2M aq NaHCO₃, water, and brine. The organic layer was dried with Na₂SO₄ and the solvent was evaporated. The crude product was purified *via* sgc using EtOAc as the mobile phase. The resulting material was dissolved in EtOAc and a solution of HCl/Et₂O was added. The solvents were evaporated to give 145 mg (42%) of Compound XXXXIV as a solid.

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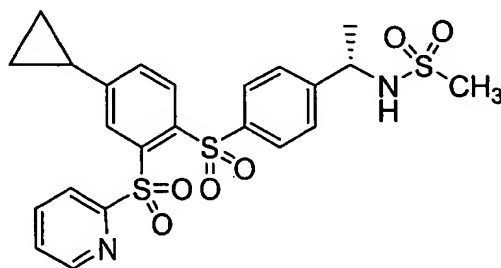
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Compound XXXXV

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Compound XXXXXV. Compound XXXV (0.92 g, 1.67 mmol), was dissolved in methanol (40 mL) and 1.0 M aq NaOH was added (20 mL). The reaction mixture was stirred at 70 °C for 21 h. The reaction mixture was concentrated and extracted with EtOAc. The organic layer was washed with 1 M aq HCl, water, and brine, then dried with MgSO₄. The solvent was evaporated and the crude product was purified via sgc using 25%-33% EtOAc/Hexanes as the mobile phase. Compound XXXXXV (0.82 g, 90%) was isolated as an oil.

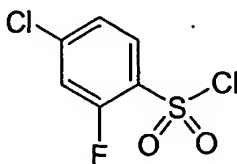
Compound XXXXV: ¹H NMR (300 MHz, CDCl₃): δ 8.56 (d, 3.9 Hz, 1H), 8.31-8.22 (m, 2H), 8.124 (d, 2.7 Hz, 1H), 8.05-7.95 (m, 1H), 7.92 (d, 8.4 Hz, 2H), 7.50-7.45 (m, 1H), 7.92 (d, 8.4 Hz, 2H), 7.27-7.23 (m, 2H), 5.8 (d, NH, 1H), 4.85-4.75 (m, 1H), 3.99 (s, 3H), 1.58 (d, 7.2 Hz, 3H).



Compound XXXXXVI

Compound XXXXXVI. Compound 50 was converted to compound XXXXXVI according to the procedure in Example II.

Compound XXXXXVI: ¹H NMR (300 MHz, CDCl₃): δ 8.56-8.52 (m, 1H), 8.31-8.23 (m, 3H), 8.02-7.90 (m, 4H), 4.87-4.78 (d, 7 Hz, 1H), 4.69 (m, 1 H), 2.66 (s, 3H), 2.16-2.06 (m, 1H), 1.51 (d, 7 Hz, 3H), 1.27 -1.17 (m, 2H), 0.96-0.90 (m, 2H).



Compound 53

Compound 53. 2-fluoro-4-chloroaniline (22.90 g, 151 mmol) was dissolved in 120 mL of AcOH and 80 mL of concentrated HCl was added with stirring. The

- 100 -

reaction mixture was cooled to 0 °C and a solution of NaNO₂ (27.2 g, 0.4 mol) dissolved in 40 mL of H₂O was added over 10 min. The reaction mixture was stirred for 30 min at 0 °C. In a separate flask, 500 mg of CuCl was dissolved in 200 mL of AcOH. The flask was cooled to 0 °C and SO₂ gas was bubbled into the solution for 40
5 minutes. The contents of the "aniline" flask were added to the contents of the second flask over 20 minutes causing a vigorous evolution of gas. After the addition was complete, the ice bath was removed, and the reaction mixture was allowed to warm to rt. The reaction mixture was poured into 500 g of chipped ice and the resulting solids were collected, washed and dried to give 26.1 g (73%) of compound 53.

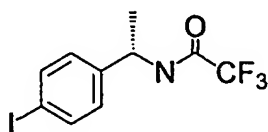
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Compound 54

Compound 54. Compound 53 (4.0 g, 17.5 mmol) was dissolved in acetone
15 (80 mL) and a solution of potassium fluoride (2.03 g, 35 mmol) in water (40 mL) was added. The reaction mixture was stirred at rt overnight. It was partially concentrated on the rotovap, then partitioned between CH₂Cl₂ and water. Evaporation of the solvent afforded Compound 54 (2.60 g, 70%) as an oil.

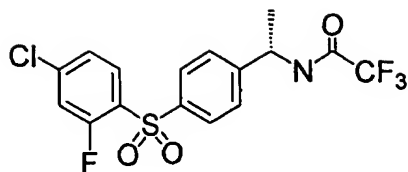
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Compound 55

Compound 55. Compound 55 was prepared from α-methyl benzylamine using a procedure similar to that used to prepare compound 1. N-Iodosuccinamide was
25 substituted for DBDMH and the product was recrystallized from isopropanol/water.

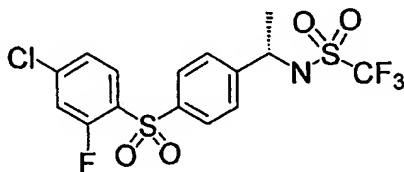
- 101 -



Compound 56

Compound 56. Compound 55 (4.33g, 12.5 mmol) was dissolved in THF (50 mL) and TMEDA (5.6 mL, 37 mmol) was added. The flask was placed under N₂ blanket and cooled to 0 °C. A solution of isopropyl magnesium chloride (2.0 M in THF, 15 mL, 30 mmol) was added via syringe over 6 min. The reaction mixture was stirred at 0 °C for 1 h. The resulting solution was transferred via cannula into a flask containing compound 53 (15 mmol) in an ice-water bath over 15 min. The reaction mixture was left stirring at 0 °C for 1.5 h. Aq NH₄Cl was added and the reaction mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried with MgSO₄. The solvents were evaporated and the crude product was purified via sgc using 1:4 EtOAc/Hexanes as the mobile phase. Solid compound 56 (3.5 g, 68%) was obtained.

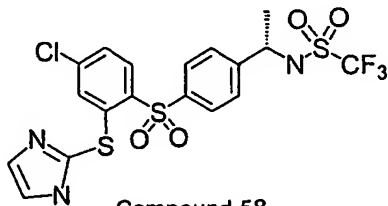
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Compound 57

Compound 57. Compound 56 was converted to compound 57 using hydrolysis and sulfonylation procedures similar to those described in Example II.

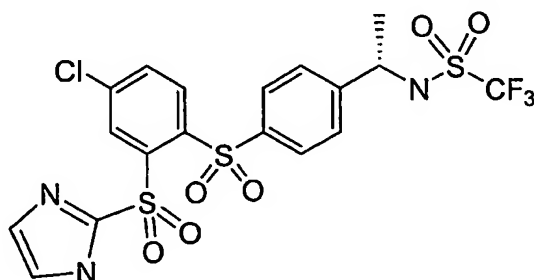
20



Compound 58

- 102 -

Compound 58. Compound 57 (0.10g, 0.22 mmol) was dissolved in 1 mL of dioxane and 2-mercaptoimidazole was added (28 mg, 0.28 mmol). Sodium hydride (60% dispersion in mineral oil, 18 mg) was added and the reaction mixture was stirred at 100 °C for 8 h. The reaction mixture was quenched with ice and extracted with
5 EtOAc. The organic layer was dried with MgSO₄ and the solvents were evaporated. The crude product was purified via sgc using a 5:95 MeOH/CH₂Cl₂ mobile phase to give 18 mg (15%) of compound 58 as product.



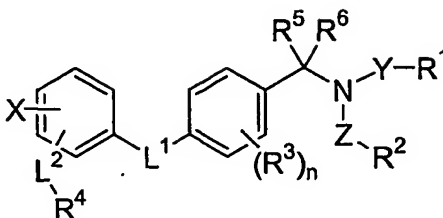
Compound XXXXXVII

Compound XXXXXVII. Compound 57 was oxidized to compound XXXXXVII
15 using a procedure similar to that used to oxidize Compound XIX to compound XXI.

It will be understood that various modifications may be made to the
embodiments and examples disclosed herein. Therefore, the above description
20 should not be construed as limiting, but merely as exemplifications of preferred
embodiments. Those skilled in the art will envision various modifications within the pe
and spirit of the claims appended hereto.

We claim:

1. A compound of the formula



5

a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein:

- R^1 is H, alkyl, haloC₁-C₆ alkyl, cycloalkyl, cycloalkylNH-, arylalkyl, heterocycloalkyl, heteroaryl, N(R²)₂, or NR²aryl, unsubstituted aryl or aryl substituted with one to three X;

R^2 is the same or different in each occurrence and is independently selected from H or C₁-C₆ alkyl;


R^3 is H, C₁-C₆ alkyl, Cl, F, CF₃, OCF₂H, OCF₃, OH or C₁-C₆ alkoxy;


- R^4 is H, C₁-C₆ alkyl, C₁-C₆ alkoxy, cycloalkyl, alkenyl, aryl, benzyl, heteroaryl, heterocycloalkyl, arylNH-, heteroarylNH-, cycloalkylNH-, N(R²)₂, or NR²aryl, said alkyl, alkoxy, cycloalkyl, alkenyl, phenyl or heteroaryl optionally substituted with one to three X;

R^5 is H or C₁-C₆ alkyl;

- R^6 is H or C₁-C₆ alkyl; or

R^5 and R^6 taken together with the carbon atom form a carbonyl group;

L^1 is C₁-C₆ alkylene, C₂-C₆ alkenylene, C(R²)₂, , -CHOR²-, NOR⁵-, -SO₂-, -SO-, -S-, -O-, -NR²-, -C(O)NR²-, -NR²C(O)-, -CHCF₃- or -CF₂-;

- L^2 is a covalent bond, C₁-C₆ alkylene, -C(R²)₂-, , -CHOR²-, -C(R²)OH, NOR⁵-, -SO₂-, -NR²SO₂-, -SO-, -S-, -O-, -SO₂NR²-, -N(R²)-, -C(O)NR²- or -NR²C(O)-;

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X is the same or different, and is independently selected from H, halogen, CF_3 , CN, OCF_2H , OCF_2CF_3 , OCF_3 , OR^2 , $\text{C}_1\text{-C}_6$ alkyl, cycloalkyl, cycloalkoxy, $\text{C}_1\text{-C}_6$ alkoxy, alkoxy $\text{C}_1\text{-C}_6$ alkoxy, O-cycloalkyl, cycloalkylamino, cycloalkylalkoxy, heteroalkyl, - OSO_2R^2 , - COOR^2 , - $\text{CON}(\text{R}^2)_2$, NHR^2 , arylNH- , $\text{N}(\text{R}^2)_2$, or NR^2 aryl;

5 Y is a covalent bond, $-\text{CH}_2-$, $-\text{SO}_2-$, or ;

Z is a covalent bond, $-\text{CH}_2-$, $-\text{SO}_2-$ or ; or

Y, R^1 , Z and R^2 can be taken together with the nitrogen atom to form a heterocycloalkyl; with the proviso that if Y is a covalent bond, R^1 cannot form a N-N bond with the nitrogen atom; and

10 n is an integer of 0 to 4.

2. A compound according to claim 1 wherein

15 L^1 is $-\text{SO}_2-$, $-\text{CH}_2-$, $-\text{CHCH}_3-$, , $-\text{C}=\text{NOR}^2-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CHOH}-$, $-\text{O}-$, $-\text{S}-$ or $-\text{S}=\text{O}$;


L^2 is $-\text{SO}_2-$, , $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, , $-\text{NH}-$, $-\text{O}-$, $-\text{NHSO}_2-$, $-\text{NHC}(\text{O})-$ or ;

20 R^1 is H, $-\text{CH}_3\text{NH}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{NHC}_3\text{H}_7$, $-\text{NHC}_2\text{H}_6$, $-\text{NHC}_4\text{H}_9$, $\text{C}_1\text{-C}_6$ alkyl, $-\text{CF}_3$, $-\text{CH}(\text{CH}_3)_2$, thiophenyl, morpholinyl, cyclopropanyl, benzyl, naphthyl, $\text{C}(\text{CH}_3)_3$, NHphenyl, 3,5-difluorophenyl, phenyl, N-cyclopentyl or $\text{N}(\text{CH}_3)_2$;

R^2 is H or CH_3 ;

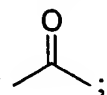
25 R^4 is furanyl, pyridyl, pyrimidyl, thiophenyl, quinolyl, t-butoxy, alkoxy, cyclohexyl, phenyl, tolyl, C_3H_7 , dimethylpyrimidyl, trifluoromethoxyphenyl, morpholinylphenyl or CH_3 ; with the proviso that when R^4 is t-butoxy, L^2 must be

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 $-\text{CH}_2-$, $-\text{CHCH}_3-$, $-\text{C}(\text{CH}_3)_2-$ or $-\text{C}(\text{CH}_2)=\text{CH}_2-$, all of the above optionally substituted with one to three substituents, which are the same or different and are independently selected from X;

R^5 and R^6 are independently H or CH_3 ;

5 X is H, Cl, CF_3 , OCH_3 , OCF_3 , OCF_2H , CH_3 or $\text{C}_1\text{-C}_6$ cycloalkyl;

Y is $-\text{SO}_2-$ or ;

Z is a covalent bond; or

R^1 , Y, R^2 and Z taken together with the nitrogen atom form a morpholinyl group.

10

3. The compound according to claim 2 wherein

L^1 is $-\text{SO}_2-$ or $-\text{CH}_2-$;

L^2 is $-\text{SO}_2-$;

15 R^1 is CH_3 or CF_3 ; and

R^4 is phenyl, pyrimidyl or pyridyl, each of said phenyl, pyrimidyl or pyridyl optionally substituted with one to three substituents which are the same or different, and are independently selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, OH, CF_3 and halogen.

20

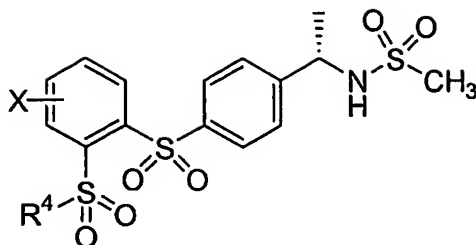
4. The compound according to claim 3 wherein the phenyl in R^4 is substituted with OCH_3 or halogen.

5. The compound according to claim 4 wherein the halogen is selected from fluorine and chlorine.

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6. The compound according to Claim 1 of the formula

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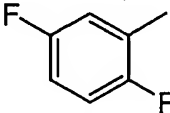
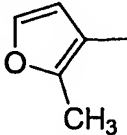
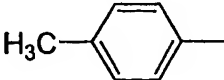
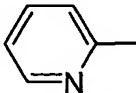
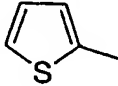
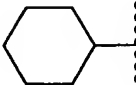
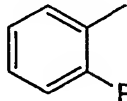
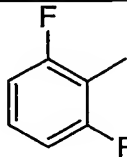
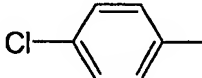
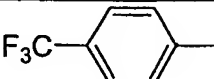
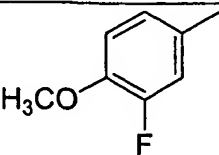


a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug;

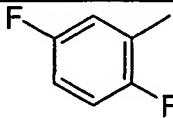
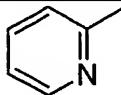
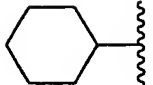
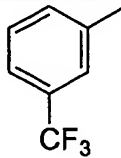
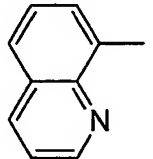
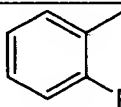
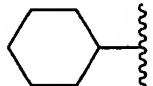
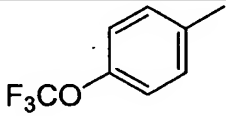
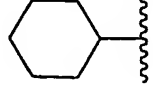
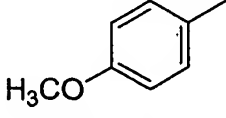
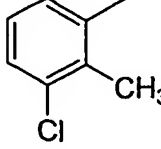
5 wherein X and R⁴ are as shown in the table below:

	X	R ⁴
	OCH ₃	
	OCH ₃	
	OCF ₂ H	
	OCH ₃	
	CH ₃	
	OCH ₃	
	OCF ₃	
	Cl	

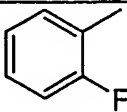
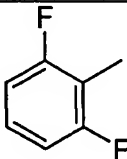
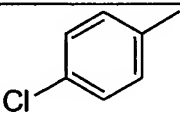
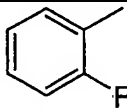
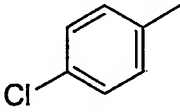
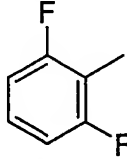
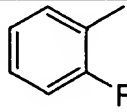
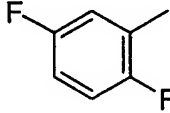
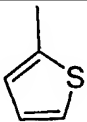
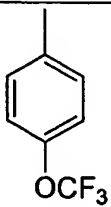
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	X	R ⁴
	Cl	
	OCH ₃	
	CH ₃	
	Cl	
	OCH ₃	
	OCH ₃	
	OCH ₃	C ₃ H ₇
	CF ₃	
	CF ₃	
	CF ₃	
	CF ₃	
	Cl	

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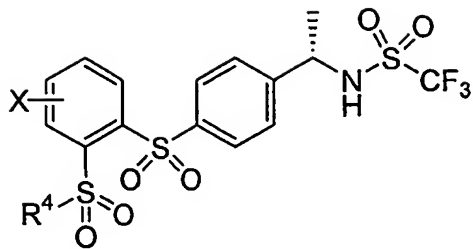
	X	R ⁴
	Cl	
	Cl	
	Cl	
	Cl	
	Cl	
	Cl	C ₃ H ₇
	OCF ₃	
	OCF ₃	
	OCF ₃	
	OCH ₃	
	OCH ₃	
	CH ₃	

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	X	R ⁴
	Cl	
	Cl	
	OH	
	OH	
	OCF ₂ H	
	H	
	H	
	H	
	H	
	H	

7. The compound according to Claim 1 of the formula

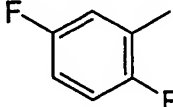
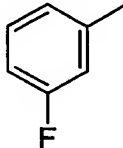
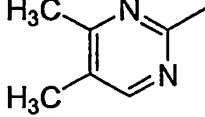
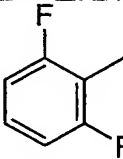
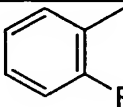
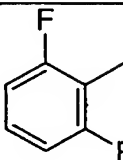
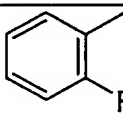
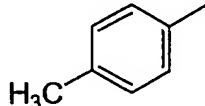
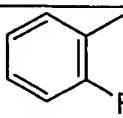
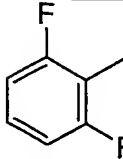
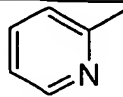
- 110 -



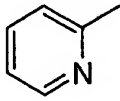
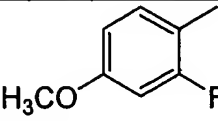
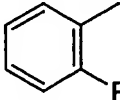
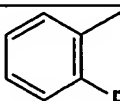
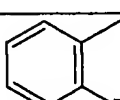
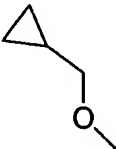
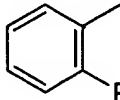
- a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of
- 5 the compound or of said prodrug;
- wherein X and R⁴ are as shown in the table below:

	X	R ⁴
	CF ₃	
	Cl	
	Cl	
	CF ₃	
	CF ₃	
	CF ₃	

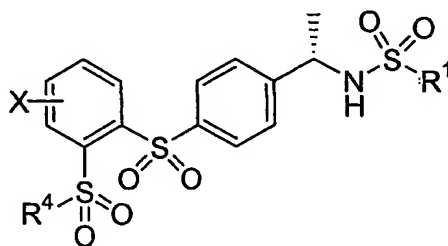
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	Cl	
	Cl	
	Cl	
	Cl	
	OCF ₃	
	OCH ₃	
	CH ₃	
	CH ₃	
	H	
	H	
	Cl	

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	CF ₃	
	Cl	
	OCH ₃	
	OH	
	OCH(CH ₃) ₂	
		

8. The compound according to Claim 1 of the formula



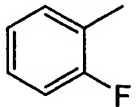
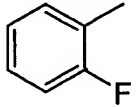
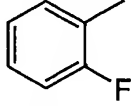
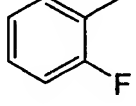
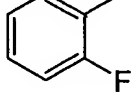
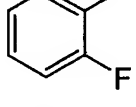
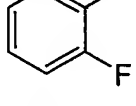
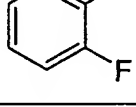
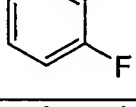
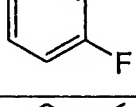
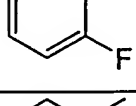
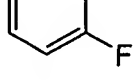
5

a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug;

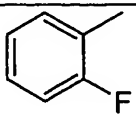
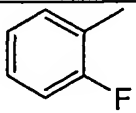
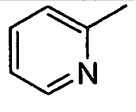
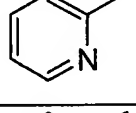

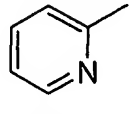

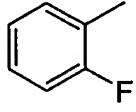

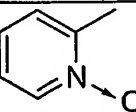
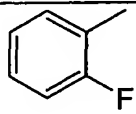
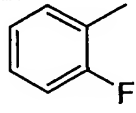
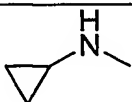
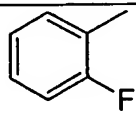
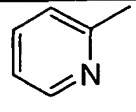
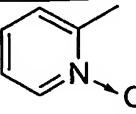
wherein X, R¹ and R⁴ are as shown in the table below:

10

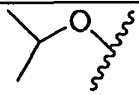
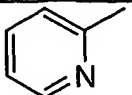
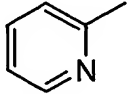
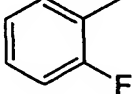
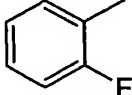
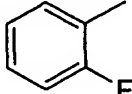
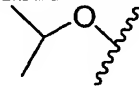
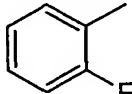
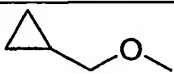
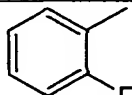
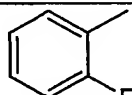
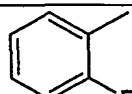
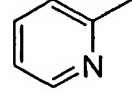

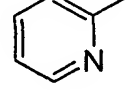
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	X	R ¹	R ⁴
	OCH ₃	CH ₃	
	OCF ₂ H	CH ₃	
	CH ₃	CH ₃	
	Cl	CH ₃	
	CF ₃	CF ₃	
	Cl	CF ₃	
	CF ₃	CH ₃	
	Cl	N(CH ₃) ₂	
	OCF ₃	CH ₃	
	OCF ₃	CF ₃	
	CH ₃	CF ₃	
	Cl	CH ₃	

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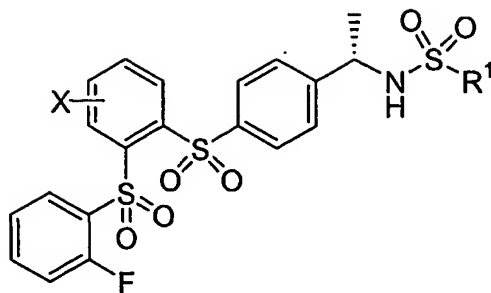
	X	R ¹	R ⁴
	H	CH ₃	
	H	CF ₃	
	Cl	CF ₃	
	CF ₃	CF ₃	
		CF ₃	
		CF ₃	
		CF ₃	
	CN	CF ₃	
	NH ₂	CF ₃	
		CF ₃	
	Cl	CF ₃	
	Cl	CF ₃	

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	X	R ¹	R ⁴
		CF ₃	
	CN	CF ₃	
	-CONH ₂	CF ₃	
	-OCH ₃	CF ₃	
	-OH	CF ₃	
		CF ₃	
		CF ₃	
	H ₃ C-CH ₂ -O-	CF ₃	
	H ₃ C-O-CH ₂ -CH ₂ -O-	CF ₃	
	OCH ₃	CF ₃	
		CH ₃	

9. The compound according to Claim 1 of the formula

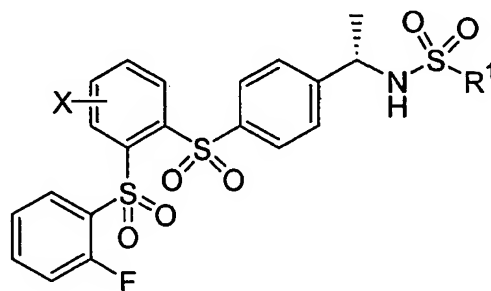
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a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is OCH₃ and R¹ is CH₃.

5

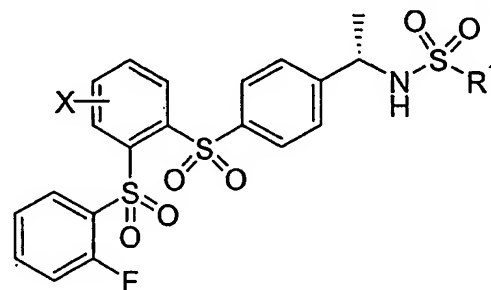
10. The compound according to Claim 1 of the formula



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is OCF₂H and R¹ is CH₃.

10

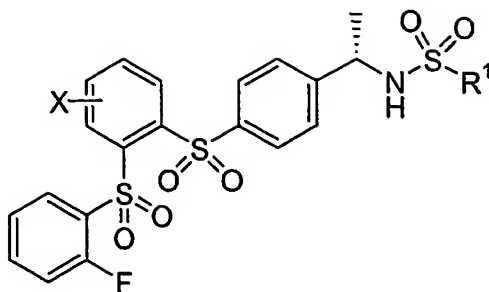
11. The compound according to Claim 1 of the formula



15 a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is CH₃ and R¹ is CH₃.

12. The compound according to Claim 1 of the formula

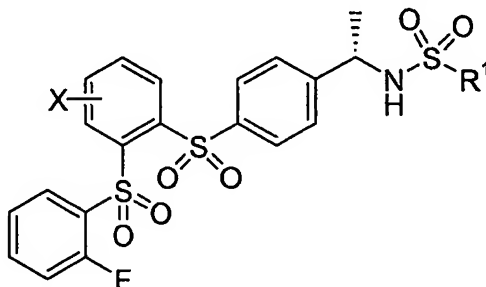
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a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is Cl and R¹ is CH₃.

5

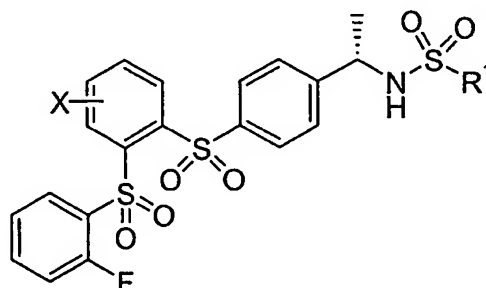
13. The compound according to Claim 1 of the formula



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is CF₃ and R¹ is CF₃.

10

14. The compound according to Claim 1 of the formula

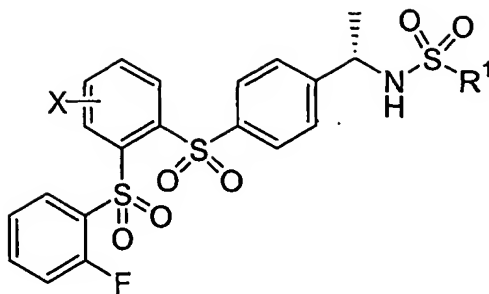


a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is Cl and R¹ is CF₃.

15

15. The compound according to Claim 1 of the formula

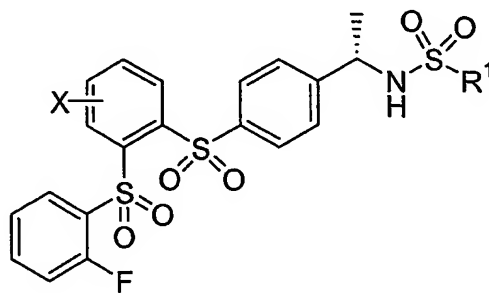
- 118 -



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is CF₃ and R¹ is CH₃.

5

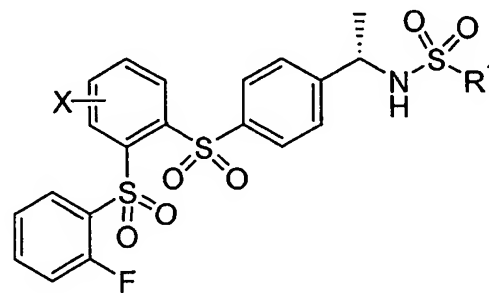
16. The compound according to Claim 1 of the formula



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is Cl and R¹ is N(CH₃)₂.

10

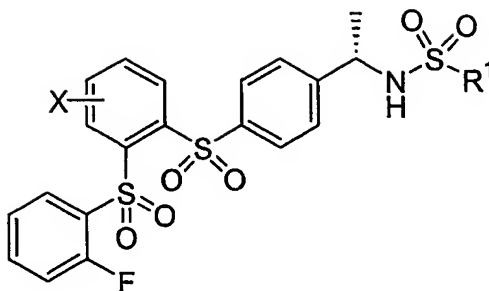
17. The compound according to Claim 1 of the formula



15 a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is OCF₃ and R¹ is CH₃.

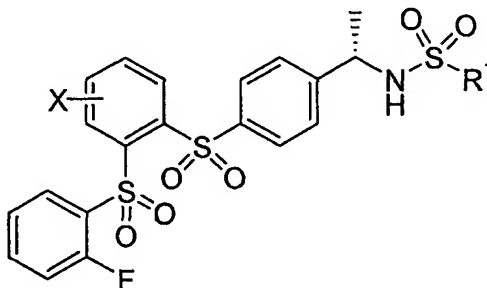
18. The compound according to Claim 1 of the formula

- 119 -



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of
 5 the compound or of said prodrug; wherein X is OCF₃ and R¹ is CF₃.

19. The compound according to Claim 1 of the formula

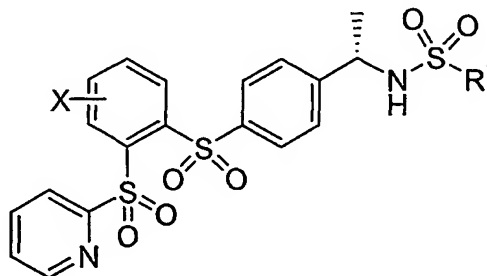


10

a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of
 the compound or of said prodrug; wherein X is CH₃ and R¹ is CF₃.

20. The compound according to Claim 1 of the formula

15

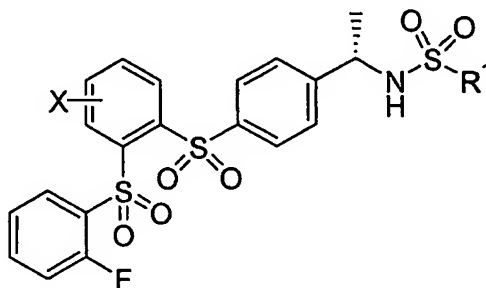


- 120 -

a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is cyclopropyl and R¹ is CF₃.

21. The compound according to Claim 1 of the formula

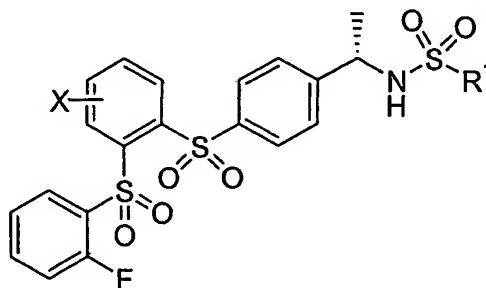
5



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is H and R¹ is CH₃.

10

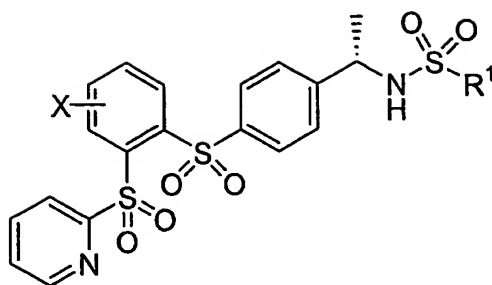
22. The compound according to Claim 1 of the formula



15 a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is H and R¹ is CF₃.

23. The compound according to Claim 1 of the formula

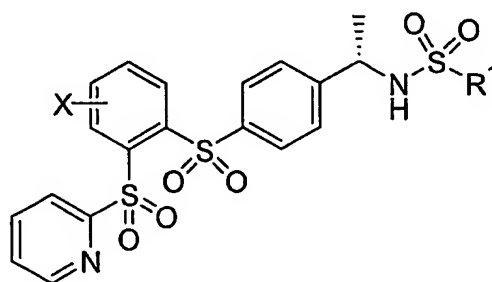
- 121 -



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is Cl and R¹ is CF₃.

5

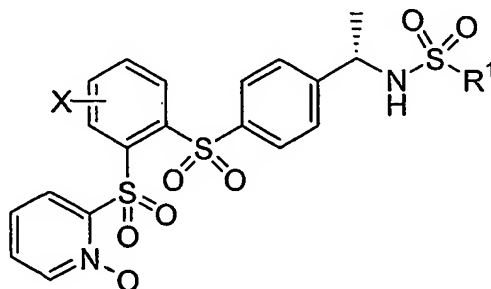
24. The compound according to Claim 1 of the formula



10 a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is CF₃ and R¹ is CF₃.

25. The compound according to Claim 1 of the formula

15

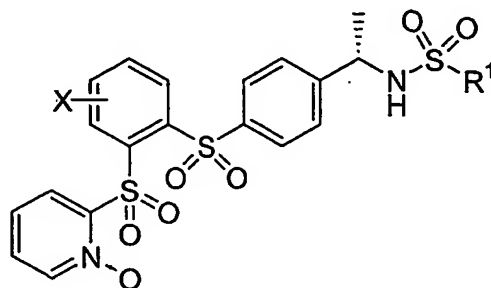


- 122 -

a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is cyclopropyl and R¹ is CF₃.

26. The compound according to Claim 1 of the formula

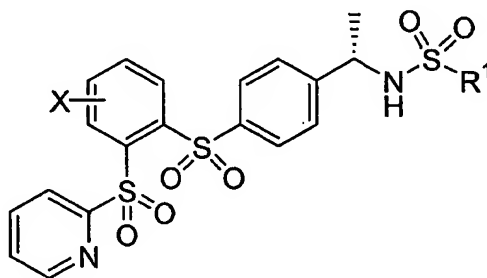
5



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is Cl and R¹ is CF₃.

10

27. The compound according to Claim 1 of the formula



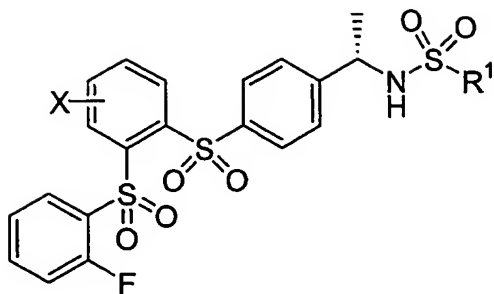
15

a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is cyclopropyl and R¹ is CH₃.

28. The compound according to Claim 1 of the formula

20

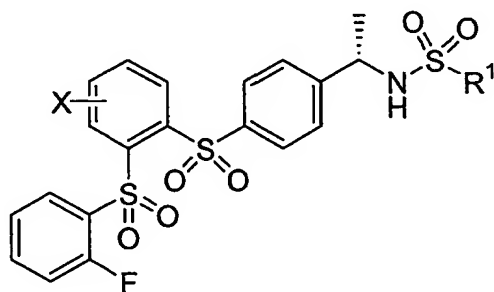
- 123 -



a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is cyclopropyl and R¹ is CF₃.

5

29. The compound according to Claim 1 of the formula



10 a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug; wherein X is cyclopropyl and R¹ is CH₃.

30. A pharmaceutical composition comprising an effective amount of a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or
15 stereoisomer of the compound or of said prodrug, according to claim 1 and a pharmaceutically acceptable carrier.

31. A pharmaceutical composition comprising an effective amount of a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or
20 stereoisomer of the compound or of said prodrug, according to claim 7 and a pharmaceutically acceptable carrier.

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32. A method of stimulating cannabinoid CB₂ receptors in a mammal comprising administering to a mammal having CB₂ receptors an effective CB₂ receptor stimulating amount of a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug,
5 according to Claim 1.

33. A method of treating cancer, inflammatory diseases, immunomodulatory diseases, or respiratory diseases comprising administering to a mammal in need of such treatment an effective amount of a compound, a prodrug
10 thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, according to claim 1.

34. A method of treating cutaneous T cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, sepsis, shock, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary
15 dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing alveolitis, psoriasis, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, Crohn's disease, inflammatory bowel disease, reversible
20 airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD), bronchitis, colitis, coronary artery disease, melanoma, transplant rejection, graft versus host disease, Hashimoto's thyroiditis, Graves disease, myasthenia gravis or Goodpasture's syndrome comprising administering to a mammal in need of such treatment an effective amount of a compound, a prodrug
25 thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, according to claim 1. .

35. The method of claim 32 wherein the condition or disease treated is selected from rheumatoid arthritis, multiple sclerosis, seasonal allergic rhinitis and
30 chronic obstructive pulmonary disease.

36. A pharmaceutical composition made by combining the compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the

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compound or of said prodrug, of Claim 1 and a pharmaceutically acceptable carrier therefor.

37. A process for making a pharmaceutical composition comprising
5 combining a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, of Claim 1 and a pharmaceutically acceptable carrier.

38. A method of treating rheumatoid arthritis which comprises co-
10 administration of a compound selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of rheumatoid arthritis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 1.

39. A method of treating rheumatoid arthritis which comprises co-
15 administration of a compound selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, an anti-TNF- α compound, a PDE IV inhibitor or other classes of compounds indicated for the treatment of rheumatoid arthritis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt,
20 solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 7.

40. The method of Claim 38 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

25 41. The method of Claim 39 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

42. A composition for treating rheumatoid arthritis which comprises a compound selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of rheumatoid arthritis and a compound, a
5 prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 1.

43. A composition for treating rheumatoid arthritis which comprises a compound selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor,
10 an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of rheumatoid arthritis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 7.

15 44. The composition of Claim 42 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

20 45. The composition of Claim 43 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

25 46. A method of treating multiple sclerosis which comprises co-administration of a compound selected from Avonex, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 1.

30 47. A method of treating multiple sclerosis which comprises co-administration of a compound selected from Avonex, Betaseron, Copaxone or other

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compounds indicated for the treatment of multiple sclerosis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 7.

5 48. A composition for treating multiple sclerosis which comprises a compound selected from Avonex, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 1.

10

 49. A composition for treating multiple sclerosis which comprises a compound selected from Avonex, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 7.

15

 50. A method of treating psoriasis which comprises co-administration of a compound selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 1.

20

 51. A method of treating psoriasis which comprises co-administration of a compound selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 7.

25

 52. The method of Claim 50 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

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53. The method of Claim 51 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

54. A composition for treating psoriasis which comprises a compound
5 selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 1.

10 55. A composition for treating psoriasis which comprises a compound selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and a compound, a prodrug thereof, or a pharmaceutically acceptable salt, solvate or stereoisomer of the compound or of said prodrug, as defined in Claim 7.

15

56. The composition of Claim 54 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

20 57. The composition of Claim 55 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/03672

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C317/50 C07C323/65 C07C317/48 C07C323/63 C07C323/43
 C07C317/22 C07C317/36 C07C317/46 C07C317/32 C07C317/44
 C07D213/71 C07D213/70 C07D233/84 A61K31/4402 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 37061 A (RADDATZ SIEGFRIED ;ROCK MICHAEL HAROLD (DE); SCHUHMACHER JOACHIM () 27 August 1998 (1998-08-27) page 135 -page 136; example 9; table 1 page 140; example 42 page 156; example 95 page 181 -page 182; examples 161-164; table 10 ---	2
A	EP 1 184 366 A (NOMURA MASAHIRO, RYORIN PHARMACEUTICAL) 6 March 2002 (2002-03-06) page 30 -page 32; examples 72-74,79-81,93,94; table 7 page 34; examples 114-116,121-123; table 8 ---	2
A	EP 1 207 157 A (KYORIN SEIYAKU KK) 22 May 2002 (2002-05-22) page 7; examples 4-6,10; table 1 ---	2
	--- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

19 June 2002

Date of mailing of the international search report

01/07/2002

Name and mailing address of the ISA

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Authorized officer

Bedel, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/03672

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/16 A61K31/435 A61P37/02 A61P37/08 A61P29/00
A61P17/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PATENT ABSTRACTS OF JAPAN vol. 2000, no. 08, 6 October 2000 (2000-10-06) & JP 2000 143650 A (TAKEDA CHEM IND LTD), 26 May 2000 (2000-05-26) abstract</p> <p>-----</p>	2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

19 June 2002

Date of mailing of the international search report

Name and mailing address of the ISA

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Bedel, C

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 32-35,38-41,47,50-53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 32-35,38-41,47,50-53

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 1

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim is impossible. Consequently, the search has been restricted to the subject-matter of claim 2.

Namely the compounds as defined in claim 2 and their coresponding use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/03672

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 32-35, 38-41, 47, 50-53
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/03672

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9837061	A	27-08-1998	DE 19740785 A1	27-08-1998
			AU 735137 B2	05-07-2001
			AU 6396598 A	09-09-1998
			BG 103646 A	29-02-2000
			BR 9807848 A	21-03-2000
			CN 1253545 T	17-05-2000
			CZ 9902979 A3	15-12-1999
			WO 9837061 A1	27-08-1998
			EP 0966436 A1	29-12-1999
			JP 2001515470 T	18-09-2001
			NO 994014 A	12-10-1999
			NZ 337331 A	25-05-2001
			PL 335194 A1	10-04-2000
			TR 9902012 T2	21-01-2000
			US 6262112 B1	17-07-2001
			ZA 9801419 A	24-08-1998
			HU 0001111 A2	28-08-2000
EP 1184366	A	06-03-2002	JP 2001055367 A	27-02-2001
			AU 5106700 A	28-12-2000
			BR 0011734 A	05-03-2002
			EP 1184366 A1	06-03-2002
			NO 20016001 A	11-02-2002
			WO 0075103 A1	14-12-2000
EP 1207157	A	22-05-2002	AU 6594700 A	19-03-2001
			EP 1207157 A1	22-05-2002
			WO 0114351 A1	01-03-2001
JP 2000143650	A	26-05-2000	NONE	